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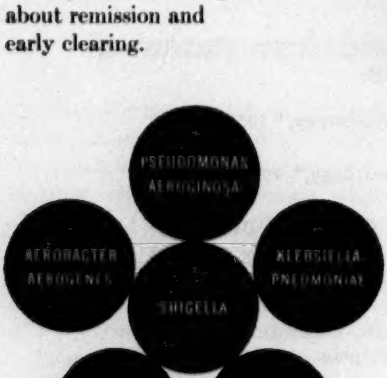

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*Food For Your Heart, a Manual for Patient and Physician, Department of Nutrition, Harvard School of Public Health, Harvard University, The American Heart Association, Inc., New York, 1952. Copies available through local Heart Association.

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1. Carithers, H. A.: J. Pediat, 38:654 (May) 1951

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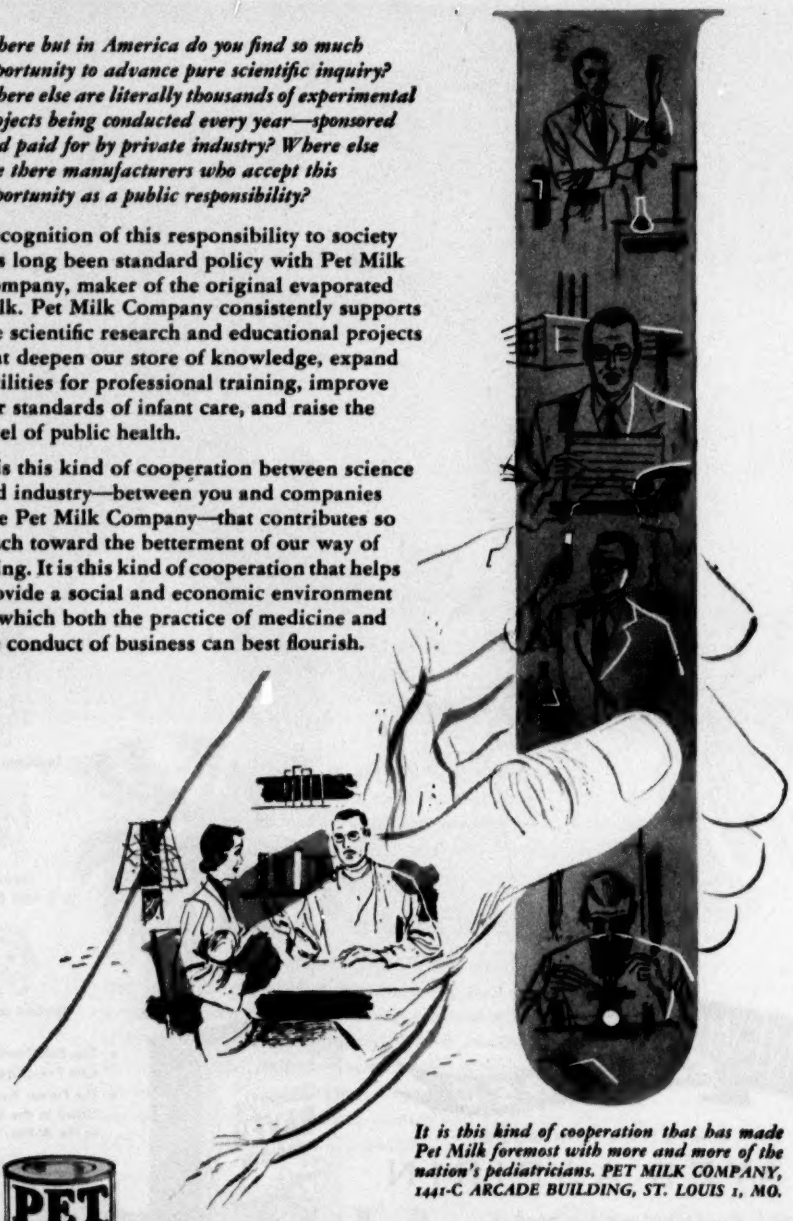

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A. M. A.
American Journal of Diseases of Children

VOLUME 85 MARCH 1953 NUMBER 3

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PURPURA IN INFANTS AND CHILDREN

Its Natural History

DAVID H. CLEMENT, M.D.
NEW HAVEN, CONN.
AND
LOUIS K. DIAMOND, M.D.
BOSTON

IN RECENT years, the increasing frequency of the occurrence of purpura in childhood has made more important an understanding of the natural history of the disease and the problem of proper management of these patients. Opinion has varied from the one extreme of doing nothing or as little as possible, in the hope that the child will "outgrow" a tendency to bruise easily or bleed freely after minimal trauma, to the other of urging radical treatment such as early splenectomy because of the danger of uncontrollable and possibly fatal hemorrhage. Each course may be defended on the basis of personal experience with one or a few patients. A pediatrician may be impressed by the number of children who have relatively little trouble with purpura and recover in a few weeks or months and decide no surgical treatment is ever needed. A surgeon who is called upon to operate on a child with intractable bleeding may be gratified by the prompt improvement following splenectomy and therefore favor operative intervention in all cases. A larger experience makes it apparent that no single method of attack is uniformly successful in all patients with a complaint having so many possible underlying causes and variations in course and severity.

Purpura in childhood is a variable symptom-complex. It may be due to a large number of different and even entirely dissimilar etiologic agents which must be sought and identified to institute proper treatment. The diagnosis of purpura haemorrhagica has been accepted far too readily when there were present as reasons for bleeding such widely different causes as acute sepsis, scurvy, hemophilia, or leukemia. Where the basic cause cannot be found, the natural history of the disease must be known in order to decide what therapy may be indicated and, more important, in order to be able to evaluate the results of any therapeutic trials.

Unfortunately very little has been published about purpura in infants and children. Differences in the course of the syndrome in the young in contrast to that in the adult are real and make a separate consideration worth while. In 1932 McLean [1]

This study was supported by a grant from the Variety Club of New England.

Fellow in Hematology, supported in part by the Commonwealth Fund of New York and the Charles P. Hood Foundation of Boston (Dr. Clement).

From the Department of Pediatrics, Harvard Medical School and the Infants' and Children's Hospitals and the Hematology Research Laboratory, Children's Medical Center, Boston.

1. McLean, S.; Kreidel, K., and Caffey, J.: Hemorrhagic Thrombocytopenia in Childhood: Clinical Study of 21 Cases, J. A. M. A. **98**:387-393, 1932.

reported on 21 childhood patients with a short follow-up, and in 1938 one of us (L. K. D.) summarized briefly [2] the results of therapy in 28 pediatric patients.

There has been a definite increase in frequency of the symptom-complex of easy bruising and free bleeding as shown by a brief review of the incidence of purpura or a hemorrhagic diathesis in patients admitted to this hospital. In 1927 the number was 8, whereas in 1951 the number was 31. This almost fourfold increase has been noted in other clinics.

No attempt will be made in this report to offer a comprehensive classification of the hemorrhagic states. In many instances the etiology and pathogenesis cannot be determined, and therefore classification can only be tentative. From a practical standpoint it seems sufficient to subdivide the symptom-complex of purpura into three major groups as follows: (1) the symptomatic or definitely secondary purpuras associated with a variety of recognizable disease entities; (2) the nonthrombopenic or vascular purpura having as a probable basis a disturbance involving the capillaries alone, possibly a sensitization phenomenon, and usually called the anaphylactoid, allergic, or Henoch-Schoenlein type, and (3) the thrombopenic form of purpura haemorrhagica, not associated with a recognized primary cause and therefore usually labeled idiopathic.

With these three simple subdivisions it is possible to classify most of the cases of purpura and, more important, to separate them into each of these large groups which may suggest certain therapeutic attempts.

As to the symptomatic or secondary purpuras, these may be either thrombopenic or nonthrombopenic. In both the thrombopenic and the nonthrombopenic symptomatic types acute infection must be considered a prime cause and excluded before any other diagnosis is accepted, particularly in these days of successful chemotherapy. Most commonly, septicemia, pharyngitis, otitis, mastoiditis, sinusitis, pneumonia, and pyelonephritis in childhood may have associated purpura. Often the striking skin manifestations of the bleeding tendency and the lack of hyperpyrexia or localizing signs of infection focus attention on the purpura to the neglect of the necessary search for the underlying infection. This has happened so frequently and infection is statistically so important a cause for purpura that it must be sought in every case. Chemical (drug) poisoning must always be excluded since many of the present-day medicinal and nonmedicinal preparations contain benzene-ring compounds and other agents toxic to the bone-marrow elements. Blood dyscrasias such as aplastic anemia, leukemia, and megaloblastic anemia may be manifested first by thrombopenic purpura. Malignant disease with metastases to the bone marrow may produce similar thrombopenic states. Congestive splenomegaly, due either to disease in the spleen itself or obstruction in the splenoportal venous system, is often first suggested by the occurrence of purpuric symptoms. Each of these may be detected by an accurate history, a complete physical examination, and careful study of the peripheral blood and, where indicated, of material from bone marrow aspiration.

In the secondary purpuras associated with changes in capillary walls (nonthrombopenic) infections again rank as an important cause. Chemical poisoning, avitaminoses, chronic disease of the kidney, heart, and liver, and congenital telangiectasia must be considered as rarer causes.

2. Diamond, L. K.: Indications for Splenectomy in Childhood: Results in 51 Operated Cases, Surgery **39**:400-421, 1938.

Hemorrhagic manifestations are frequently associated with primary disturbances in blood-clotting elements. Of these, hemophilia is best known and can be differentiated by accurate and careful determinations of the clotting time performed on cleanly-drawn samples of venous blood and by prothrombin consumption tests. Prothrombin deficiency requires exclusion by controlled estimates of the prothrombin level. Fibrinogen deficits, either secondary to liver disease or to a congenital and hereditary defect, hemorrhagic diatheses such as "pseudohemophilia," Von Willebrand's disease, and certain of the rare deficiencies of recently-discovered clotting factors (Factor 5 of Owren, Factor 6 [S. P. C. A.], and others) must always be excluded.

Having considered all these causes for a bleeding tendency and for purpuric manifestations, it is then necessary to determine first and foremost whether one is dealing with a thrombopenic purpura of an unknown cause (commonly called idiopathic) or a nonthrombopenic anaphylactoid type of purpura. Although accurate platelet counts are certainly desirable, careful examination of well-prepared matched cover-slip smears of capillary blood may aid in this differentiation and are generally more readily available and more reliable in the hands of the average observer.

In an attempt to learn more of the natural history of purpura in infancy and childhood, the cases diagnosed as purpura in this clinic have been reviewed for the 12-year period from 1936 to 1947, inclusive. All patients with a diagnosis of purpura have been followed personally, and the children have been seen again, if possible. During this 12-year interval, approximately 173 such patients have been cared for at the Infants' and Children's Hospitals in Boston. On careful investigation, either it was found that almost a fifth of these records contained inadequate data for this study, or the patients were later shown to have other primary disease. This group was therefore rejected, leaving 140 patients with unquestionable purpura adequately investigated and followed. It is these patients who are discussed in this paper. All children in this series had the onset of symptoms before the age of 12 years.

DISTRIBUTION

There was an average of 10 cases a year during the decade from 1936 to 1945, but there has been a definite increase recently. There are several factors which might account for this. Perhaps the most obvious is that the number of referrals of interesting hematologic problems to this clinic has increased year by year. Another possible factor is the increased use of new drugs which might cause capillary or bone-marrow damage and lead to purpura. Then again, it may be a combination of dietary, environmental, and disease factors that predisposes to the development of purpura more commonly now than heretofore. By years, the number of patients in this group is shown in Chart 1.

Age.—In about half the cases the patients had the onset of the disease by the age of 4 years. Almost a quarter of the series began in infancy, before 2 years. There appeared to be a slight tendency toward greater frequency of the disease again at about the age of 8 years. The figures are depicted in Chart 2.

In connection with congenital purpura, it was found that five patients were said to have had a history of bruising since birth. Three of these had the nonthrombopenic and two the thrombopenic variety of purpura. Only one patient, however, was followed from birth.

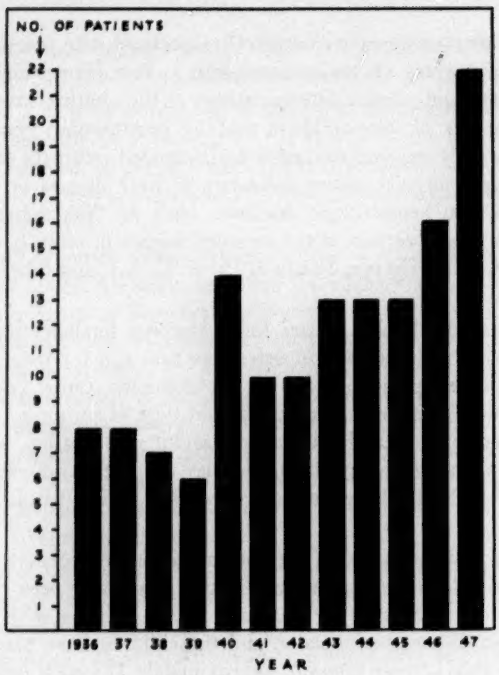

Chart 1.—Patients with purpura.

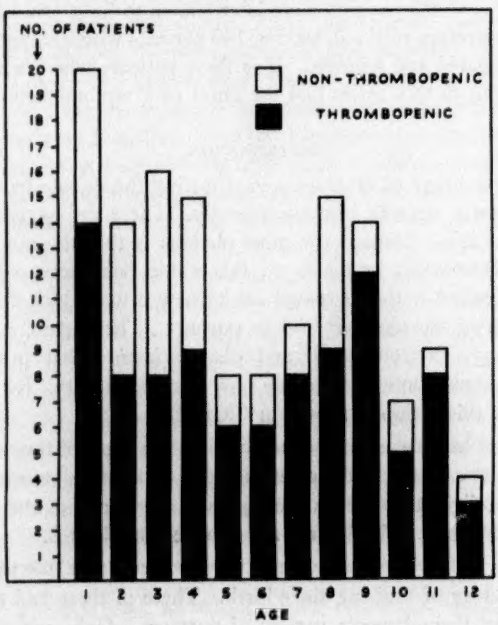

Chart 2.—Types of purpura by age.

Sex.—Unlike purpura in adults, there appeared to be no significant difference in the incidence of the disease in the two sexes.

Color and Race.—All patients in this series were white. The racial distribution conformed well to that of the outpatient clientele.

Seasonal Onset.—There was a tendency for the patients to have the onset of the purpura during the winter months. The months in which the greatest number of patients started having symptoms were January, February, March, and April. This trend was clear-cut, however, only in the thrombopenic cases. The trend is perhaps noteworthy in connection with the incidence of respiratory infections in many patients.

CLASSIFICATION

As has been explained previously, the present series has excluded a number of purpura patients suffering from other conditions such as leukemia, aplastic anemia, myelophthisic anemia, septicemia, scurvy, and chronic organic diseases primarily of other organs such as the kidney, the liver, and the heart. The cases can be classified as follows:

I. Nonthrombopenic purpura	
A. Anaphylactoid	35
B. Symptomatic	
1. Infection	1
2. Miscellaneous	8
Total	44
II. Thrombopenic purpura	
A. Idiopathic	
1. Acute (less than 6 weeks in duration)	38
2. Chronic	55
B. Symptomatic	
1. Chemical	2
2. Splenomegaly	1
Total	96

Comment.—As will be discussed subsequently, it would seem that many of our cases of "primary" purpura haemorrhagica were precipitated by infection. A temporal relationship between infection and purpura might be interpreted in some cases as coincidental and in others as causal. The arbitrary dividing line between acute and chronic was chosen as six weeks. In the chronic group is included a number of children who were followed to "cure" within several months, 10 within a year, after onset of their disease.

In connection with the nonthrombopenic patients, it will be noted that the majority of them were characterized as "anaphylactoid." In this paper, this adjective has been applied to those patients who have exhibited recurrent migrating joint pains with or without bouts of acute abdominal pain or hematuria associated with their purpuric lesions.

From the foregoing data it is apparent that among the hospitalized patients there were roughly twice as many purpuric patients with thrombopenia as those with normal platelet levels. Actually this is misleading as far as the over-all incidence of the two types of purpura is concerned. There is general agreement that vascular or nonthrombopenic purpura is more common than the thrombopenic type. Much

of the purpura seen associated with acute infection is of the nonthrombopenic type, though either variety may occur. Our data are weighted falsely in favor of the thrombopenic type because, in general, it is a more serious and protracted disease and is therefore more apt to require referral to a hospital. In private practice, more patients with vascular purpura are encountered.

NONTHROMBOPENIC PURPURA

Family History.—A tendency to bruise or bleed easily was reported among the relatives of only five patients with nonthrombopenic purpura, a statistically insignificant number.

Chief Complaint.—Easy bruising was the most prominent symptom in the 44 nonthrombopenic cases. This was true of about half the patients in this group. Second to bruising, joint pains were the most disturbing symptom for these children. In a small number of these, ecchymoses later appeared around the affected joints.

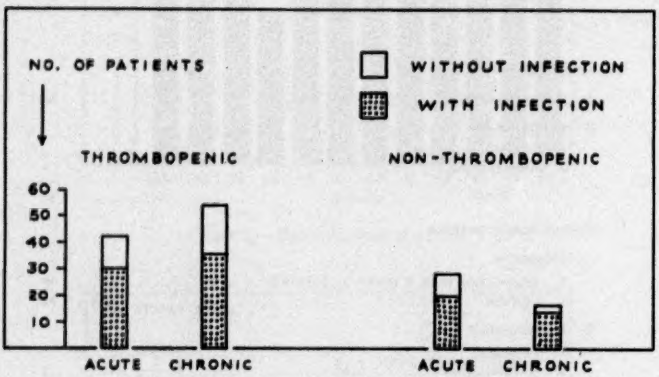

Chart 3.—Association with infection.

In five, a discrete reddish maculopapular rash was the sign that led to the hospital visit. These lesions then progressed to true ecchymoses. Nosebleed occurred in only 3 of the 44 nonthrombopenic patients.

Infection.—The development of purpura following acute infections has long been noted, especially in children. A clear-cut history of acute infection occurring in close proximity to the onset of purpura or the finding on examination of an unsuspected low-grade infection occurred in approximately 65% (91 patients) of our 140 cases (Chart 3). It is probable that this figure is an underestimation of the role of this factor in view of the frequency of infections which are not obvious in infants and children on both history and physical examination. Infection was associated with approximately two-thirds of the acute cases of purpura of both types and with about one-half of the chronic ones. In analyzing the type of infection, it becomes apparent that upper respiratory infections are by far the commonest to be followed by purpura. Among the nonthrombopenic patients, there were only five exceptions: scarlet fever, infectious mononucleosis, ulcerative colitis, hepatitis, and cellulitis.

Cultures of material from the throat and frequently from the nose and occasionally cultures of the urine in 36 of the 44 nonthrombopenic patients yielded the following results:

Hemolytic Streptococcus	16
Staphylococcus aureus	6
Hemophilus influenzae	2
Pneumococcus	1
No growth	11

The interval between the onset of an acute infection and the first appearance of purpura could be determined accurately in 28 of the nonthrombopenic patients. In a third of the patients purpuric symptoms developed during the first week and in three-fourths of them in the first 11 days following the onset of acute infections. Several exhibited purpura two weeks following a respiratory infection. In this connection, a small group of children had a history of an uncomplicated respiratory infection which was followed in 8 to 10 days by a secondary respiratory infection leading almost immediately to purpura. This "double infection," with an interval between, leads one to the attractive hypothesis that these patients may have been sensitized to a bacterial antigen which, when reintroduced, evokes a reaction of hypersensitivity with thrombopenia or abdominal or joint pains. It is interesting to note how infrequently purpura follows a single attack of a severe infection.

Fever.—Fever was not a prominent feature of either type of purpura. Rectal temperatures over 100 F. were recorded in approximately 30% of all the patients in the first few days in the hospital. The temperatures were rarely much elevated, only three being over 103 F. (rectal).

It is noteworthy that both groups of patients for the most part did not appear significantly ill on entry to the hospital. Even though their purpura was severe and extensive, the children were not usually prostrated by their illness.

Allergy.—Purpura, with and without thrombopenia, has long been regarded by some observers as a hypersensitivity phenomenon and has been found in association with classical manifestations of allergy in a significantly high number of patients.

Positive family histories for allergic manifestations were found in 11 of the 44 nonthrombopenic patients (25%). Personal manifestations of frank allergy in this group of patients were found in 13 (30%). Figures for the thrombopenic group are given elsewhere. If both groups are combined, however, positive family histories for allergic manifestations were found in 49 (29%) and personal manifestations of allergy were noted in 28 (20%).

Drugs.—For years, various medications have been blamed for the development of purpura, but generally the thrombopenic type. In neither group of patients seen during the past 12 years, however, was there convincing evidence that the purpura was definitely due to drugs.

Joint Symptoms.—Two-thirds (29) of the nonthrombopenic patients showed definite joint signs at some time or other during their illness. Frequently the pain, limitation, and swelling of their joints ushered in the bouts of purpura. Often as the swelling and pain subsided, ecchymoses appeared. These ecchymoses were sometimes confined to the involved joints, but more often were fairly generalized. Half of the patients (15) with these joint symptoms had family or personal histories

of allergy. These joint signs and symptoms were always transient, though frequently recurrent, and in no patient in this series did they lead to permanent detectable joint damage, in contrast to hemophilia.

Splenomegaly.—Enlargement of the spleen was surprisingly uncommon in patients with or without thrombopenia. No patients with nonthrombopenic purpura showed marked enlargement of the spleen. Only 3 patients of the 44 in the normal-platelet group had spleens which were regarded as enlarged. None of these, of course, was subjected to splenectomy.

Heart Involvement.—An attempt was made to determine the number of patients with structural heart defects, either congenital or acquired. As had been stated previously, patients with recognizable active rheumatic fever were excluded from the series. The problem of interpreting apical systolic murmurs is frequently difficult, and in this group it was even more so because of the frequency with which anemia, causing hemic murmurs, complicated the purpura. Estimates of heart sounds and size, therefore, were deferred until the patient was free from anemia. A number of the positive findings were obtained some years after the purpura had disappeared.

Among the 44 nonthrombopenic patients, there were only 3 who had persistent moderate medium-pitched systolic murmurs of moderate duration and of maximal intensity at the apex. There were no cases of congenital heart disease in this group. This incidence of acquired heart disease is difficult to interpret. Taken by itself, it is perhaps not significant. Coupled with the thrombopenic patients, however, the total becomes 10 patients with acquired valvular disease. This figure may be significant.

Course.—In general, the course of the disease in patients with normal platelet counts has been much more benign. In only 16 of the 44 patients was the disease regarded as chronic, with symptoms lasting more than six weeks, and in 14 of these on whom adequate follow-up was possible, good health has been maintained. One patient still bruises a little more readily than normal, but this does not curtail his activities and he has recently undergone tooth extraction without difficulty. The only other patient with any symptoms is a girl with an ileostomy for an ulcerative colitis who, although she had bouts of diarrhea, painful swelling of the joints in her hands and feet, and purpura, has now been free of these episodes for five years.

There was one group of patients with nonthrombopenic purpura who were sufficiently different in their signs, symptoms, and course to warrant separation from the rest and to deserve special consideration. These not only had recurrent bouts of abdominal and joint pains, but also episodes of gross hematuria, which usually accompanied showers of petechiae and ecchymoses in the skin. The striking renal involvement and their generally longer course differentiates them from the rest of the group. These patients have been well described by Osler[3] and other careful observers in the past 40 years. We had eight such patients, or about one-fifth of our nonthrombopenic group.

In this group there were five boys and three girls. Their ages were 3½, 5, 5, 7, 7, 7½, 7½, and 8 years. Thus the syndrome was not seen in the infants in this series. Manifestations of allergy in these patients or their families were no more

3. Osler, W.: Visceral Lesions of Purpura and Allied Conditions, Brit. M. J. 1:517-525, 1914.

prominent than in the other children. In four patients the chief complaint was joint pain, in three it was ecchymosis, and in one it was nosebleed. Fever was not present or was low-grade. Several of them not only showed crops of petechiae or ecchymoses but had skin manifestations which could best be described as a true maculopapular rash which, on fading, left the skin stained with extravasated blood. The ecchymosis was very generalized and appeared not only on the extremities but also on the trunk and in one instance on the eyelids. Gross hematuria appeared in all eight and impaired renal function was reflected by azotemia. The blood nonprotein nitrogen was elevated to an average of 70 mg. per 100 cc. in five of the six patients followed. In the sixth it was normal. In all these patients the nonprotein nitrogen level returned to normal as the urine sediment improved. All patients had heavy albuminuria which subsequently cleared completely, except one patient who still shows a small amount, but whose general health and exercise tolerance are excellent. The blood pressure was elevated in only one patient. With recovery, the blood pressure returned to normal, where it has remained for 10 years. His urine is normal. In two patients, blood was found in the stools. This melena recurred in association with visible showers of petechiae, abdominal and joint pains, and hematuria. A clinical feature observed in this group of patients is that most of them have exhibited a pallor out of all proportion to their anemia. In fact, none was markedly anemic. This pallor, furthermore, varied appreciably from day to day. This phenomenon was regarded as further evidence of diffuse vascular involvement, especially of the arterioles and capillaries of the skin. The course of this group of six patients was longer than that of the other patients with nonthrombopenic purpura. These children required three to six months before they were themselves again, according to the testimony of their mothers. The symptoms and signs of their illnesses, however, generally disappeared within two months. Despite the relatively benign course exhibited by these patients, it should be realized that vascular purpura may result in serious renal impairment and even death.

The bacteriology of this group revealed that two patients were harboring the hemolytic Streptococcus in their throats, and one Staphylococcus aureus.

As to the pathology of the syndrome, a biopsy of the skin was done for one patient. The essential lesion was an acute perivascular inflammation, with polymorphonuclear leucocytes and rare lymphocytes around the vessels of the derma. Infiltration of these cells extended moderately into the vessel walls and also for some distance into the connective tissue surrounding the vessels. This patient did not show an eosinophilia in his peripheral blood. There seemed little doubt that he had an extensive blood-vessel disease. His complete cure in a 12-year follow-up is reassuring. He is now 20 years old.

Laboratory Data.—Certain laboratory determinations were of help in diagnosis and treatment. The tests performed included a complete blood count, with a platelet count, bleeding and clotting time determinations, the tourniquet test, and a urinalysis. With these procedures done at the outset, and thereafter only certain ones repeated as indicated, satisfactory management was possible.

Hemoglobin Concentration and Red Cell Count.—In the majority of the nonthrombopenic patients, the values for the hemoglobin concentration and the red cell count were either normal or only slightly below normal, dependent on blood loss.

Leucocyte Count and Differential Count.—The total leucocyte count was generally not helpful in diagnosis or subsequent treatment. The admission count showed great variation and was profoundly affected by the presence of infection, especially in the younger patients. In general, there was a tendency for the initial count to be a little higher in the nonthrombopenic patients than in those with low platelet counts, though in both forms of the disease normal white blood counts are frequently found.

The differential leucocyte count generally gave little helpful information. On the negative side, it was always important to make certain that the thrombopenia was not associated either with a granulocytopenia or with a leukemoid blood picture, both of which suggest serious primary disease states. Eosinophilia of 5% or more was found in 14 of the 44 nonthrombopenic patients. A greater degree of eosinophilia was noted in more patients in the thrombopenic group.

Platelet Count.—The platelet count was of greatest value in the initial examination of each patient in order to differentiate the thrombopenic type of purpura from the nonthrombopenic. In every case, examination of stained films prepared on matched cover-slips helped confirm the level of platelets estimated by direct counting. Obviously thereafter the count was of interest chiefly in the thrombopenic group. In connection with the nonthrombopenic patients, it may be noteworthy that almost half of them (21) had platelet counts that were increased, or at least were above 300,000 per cubic millimeter, the upper limit of normal by the technique used. Six of these counts were 450,000 or above; the highest was 834,000 per cubic millimeter.

Bleeding and Clotting Times.—The bleeding time was generally of little help in establishing the diagnosis, which usually rested on firm ground created by the clinical picture, the platelet count, and the tourniquet test. In infants especially, difficulties in technique make this measurement occasionally unreliable. In the nonthrombopenic group, normal bleeding times were the rule.

Perhaps the greatest service rendered by clotting time determinations was in ruling out hemophilia among the male patients. Both the thrombopenic and the nonthrombopenic patients usually had coagulation times well within normal limits.

Tourniquet Test.—Among the nonthrombopenic patients, positive tourniquet tests were found in only 10%. Even in this group, however, the degree of positivity of the test tended to parallel the severity of the bruising tendency.

Urinalysis.—The majority of the patients showed no abnormalities in their urine at any time. Approximately one-fourth (12) of the 44 nonthrombopenic patients, however, did show appreciable albuminuria during the acute phase of their illness. Appreciable hematuria was noted at one time or another in 10 patients.

In spite of albuminuria and hematuria, it may be noteworthy that most patients showed no impairment of ability to concentrate the urine. Casts, coarsely granular or cellular, were noted occasionally.

In general, the renal lesion has been reversible. Pointing even more menacingly to serious renal involvement are signs of hypertension and nitrogen retention. These last two, though associated with a more severe, protracted, and occasionally fatal form of the disease, were also compatible with complete recovery in the cases reported here.

Fatal Cases.—There were no deaths among the primary idiopathic thrombopenic purpura patients and none among the anaphylactoid nonthrombopenic children, the

combined group numbering 128 cases. There were, however, five deaths among the 12 children with purpura secondary to other causes. One of these had a normal number of platelets, the other four had thrombopenia.

THROMBOPENIC PURPURA

Family History.—A tendency to bruise or bleed easily was reported among the relatives of 17 patients with thrombopenic purpura, over three times as many positive family histories as were elicited from the nonthrombopenic group. Four of the thrombopenic patients had relatives given a diagnosis of thrombopenic purpura.

Chief Complaint.—Like the nonthrombopenic patients, those with low platelet counts had as their chief complaint easy bruising in about half the cases. Among the remaining patients in the group, however, there was an interesting divergence in the signs and symptoms that brought them to the hospital. Another quarter of the patients (24) came to the hospital because of severe nosebleed. There were three different groups of five patients each who were seen because of bleeding gums, hematuria, and melena, respectively.

Infection.—As has been stated in the section on nonthrombopenic purpura, infection has been associated with an appreciable number of patients with either form of the disease. Of the 96 patients with thrombopenic purpura, 65 had an acute infection associated with the onset of their disease. The majority of these had upper respiratory infections. There were only seven exceptions. These were patients with rubella, chicken pox, infectious mononucleosis, and pyelonephritis.

The bacteriology of these 52 thrombopenic patients with infection was investigated in 39 cases. These showed the hemolytic Streptococcus to be the most common offender, with the pneumococcus second.

In 22 of the 96 thrombopenic patients the interval between the onset of infection and the first appearance of purpura was clearly defined. More than half developed purpura within a week following an acute infection. Again a small group showed a "double infection" a week or more apart, the first infection uneventful, but the second associated with purpura, suggesting an appropriate interval for development of sensitization to a bacterial antigen.

Allergy.—It was interesting to note that the increased incidence of allergic manifestations among relatives of the patients occurred in the thrombopenic cases. Among them were found family histories positive for allergy in 29 patients (30%). Personal manifestations of frank allergy in the low-platelet group of patients were noted in 14 (15.5%). These figures are well above the expected incidence of allergy in families encountered in this clinic.

Drugs.—For years thrombopenia has been linked to an increasing number of drugs. The importance of pharmaceuticals as a cause of purpura of either type was not impressive among the 140 patients whose cases are collected here.

Sulfonamide therapy was given a number of children for their acute respiratory infections. In these cases it was impossible to rule out a drug sensitivity, but there was no associated depression of granulocytes or anemia or specific dermatitis to suggest a sulfonamide reaction.

In two patients there was a history of pica with the chewing of paint. In neither of these patients did lead ingestion appear to cause the purpura. Other patients had been given a variety of medications which could not be incriminated as the cause of their illness. These included aloin, belladonna, ipecac, phenobarbital, acetylsalicylic acid, mineral oil, and calcium and sodium hypophosphites. In one patient thrombopenic purpura developed about three days after she received the third of a series of pertussis vaccine injections. This, however, had been given by her local doctor because of pertussis from which she had been suffering for a month, thus minimizing the importance of the vaccine or even of the pertussis as the cause for the purpura. She was "cured" within a year and has remained so since.

Joint Symptoms.—Unlike nonthrombopenic patients, the low platelet group of patients rarely exhibited joint symptoms during their illness. In fact, among 96 thrombopenic patients, there were only 2 who had complaints referable to the joints.

Splenomegaly.—Enlargement of the spleen was noted in only 13 of the 96 patients with thrombopenic purpura. The size of the spleen varied greatly on physical examination from being just palpable to extending several centimeters below the costal margin. Only two patients with low-platelet purpura were regarded as having markedly enlarged spleens. Their histories are noteworthy. One was a 3-month-old infant who had a rapid downhill course and died three weeks after onset with a terminal interstitial pneumonia. Infection may well have contributed to his splenomegaly. The other unusually large spleen was removed from a 4½-year-old boy who had had severe bruising for a year. He had had a pneumococcal (Type 9) primary peritonitis at the age of 5 months and shortly thereafter was first noted to have had splenomegaly. His spleen was six times the average weight for that age and histologically showed the changes typical of fibrocongestive splenomegaly.

Heart Involvement.—Among the 96 thrombopenic patients, there were 7 who showed persistent moderate medium-pitched systolic murmurs of moderate duration and of maximal intensity at the apex. (Faint murmurs were disregarded.) There were five thrombopenic patients with probable congenital heart disease, based on the known duration, type, and location of their murmurs. One of these patients had a patent ductus arteriosus which was ligated at 9 years of age, two months after a successful splenectomy was performed.

These data are difficult to interpret. If 10 patients in this series have acquired valvular disease, even though mild, it would suggest a higher incidence than is found among general hospital patients. Three patients with nonthrombopenic purpura who exhibited acquired heart disease have been described with that group. Careful examination of the heart, especially in the absence of anemia, should be an important feature of the management and follw-up of these children. It is a point on which more precise information is needed. The relationship between the rheumatic state and purpura of either type remains obscure. Of interest in this connection is another patient who was seen with thrombopenic purpura beginning at 2½ years of age. His heart was perfectly normal. More than three years after having purpura he was admitted with active rheumatic fever and now has classical mitral insufficiency of mild degree. This could, of course, represent merely a chance association of two unrelated diseases. Taken with the other patients, however, and in view of some

of the common features to the pathogenesis of purpura and rheumatic heart disease, it is possible that both represent a tendency toward development of sensitization to bacterial antigens. Careful observation of a large number of patients over several years should help clarify this point.

Course.—As has been stated previously, the duration of symptoms in patients varied enormously. Over one-third (38) of the thrombopenic group were symptom-free within six weeks after onset and were classed as having an acute condition. Another group of 19 patients had symptoms for only a year or less, a number for only a few months. Then there was a large variation in the duration of mild bruising for others varying up to 12 and 15 years.

Some patients had years of relative freedom from serious bleeding, although abnormal bruising has generally persisted. Respiratory infections frequently were associated with an exacerbation of the disease in patients in whom the disease had been relatively quiescent.

In connection with the menarche in girls who have had thrombopenic purpura, the information is rather limited but a few facts seem worth recording. The girls who had acute thrombopenic purpura as young children and then spontaneously became symptom-free after some weeks, months, or years, seem to have had no abnormal bleeding with the onset of their menses. The patients who have suffered from metrorrhagia and menorrhagia are those who had chronic thrombopenic purpura. In this series there are six girls who had chronic thrombopenic purpura in childhood who have passed through puberty and on whom we have adequate data. Two had splenectomies before puberty and four did not. They are doing well except for one who was anemic when seen recently. She had had a splenectomy. Two of the patients had prolonged, profuse, and irregular periods at the menarche, but subsequently normal flow was established. The splenectomized girl of this pair bled for a month, but later improved, and the girl with her spleen intact bled for 16 days, but is now having no difficulty. The splenectomized girls who had abnormal bleeding at the menarche were those who had been only somewhat improved following operation and whose platelet levels were still low. They were still having nosebleed and easy bruising at the time their menstrual periods began.

The difficulty at the time of the menarche seemed to parallel in severity the degree of bruising and bleeding in the patient beforehand, rather than being related to the presence or absence of the spleen. Splenectomy merely in anticipation of an approaching menarche in a patient with only a mild bruising tendency would, therefore, not seem justified. Nor does the operation appear indicated merely on the basis of a few early abnormal periods.

Mild bruising has been well tolerated by these children and, as had been stated above, at least 19 with "chronic" cases were spontaneously cured within a year. Of special interest in following these children has been their rate of growth and development. These have progressed most satisfactorily in the vast majority. In fact, a number of children who were below the 10th percentile for height and weight have been followed into positions close to the 50th percentile in spite of persistent mild bruising.

Congenital thrombopenic purpura deserves special comment. Five patients gave a history of bruising or bleeding since birth. For only one infant, however, was there

adequate information from birth. This infant was the second child born of Italian-American parents. The mother, who had bruised easily since the age of 3 and who had had severe bleeding requiring transfusions after tonsillectomy at 9 years of age, was first given a diagnosis of thrombopenic purpura when at 13 menorrhagia developed with her menarche. This continued to be such a problem that at 15 she had a splenectomy. Shortly thereafter she was married. Her benefit from splenectomy was marked but temporary. Five months postoperatively her platelet count had fallen to 24,000 per cubic millimeter. At the age of 16 she gave birth to a son by Caesarean section. His platelet count was 8,000 per cubic millimeter at one hour of age, but his only hemorrhagic sign was mild rectal bleeding, at one month of age for two days. His platelet count gradually rose until at the age of 2½ months the level reached 280,000 per cubic millimeter. He has been well since. Our patient was a boy born two years later. He had a few ecchymoses on his face. His platelet count at one hour of age was 11,000 per cubic millimeter. The count ranged from 8,000 to 20,000 per cubic millimeter during the first 12 days. When he was 3 days old, he showed small amounts of blood in his stools and a few purpuric spots on his body. Six days later he was admitted to the Infants' Hospital, where he remained a month. He received four transfusions in the first week and three in the second week of hospitalization. There were no evidences of further bleeding. The stools gradually became free of blood. The platelet count slowly rose to 134,000 per cubic millimeter by the age of 11 weeks. The child is now 5 years old and has remained symptom-free. It is interesting that this same mother has since given birth to another son who has followed a similar but even milder course. This family has since been reported by Epstein and co-workers.[4]

Hemoglobin Concentration and Red Cell Count.—Severe anemia was noted in a small number of patients, but it was related to extent of blood loss. There were six who had hemoglobin concentrations of 5.5 gm. per 100 cc. (35%) or below. Of the 22 children with appreciable anemia, two-thirds (14) had the thrombopenic type of purpura. This form of the disease generally presents the greater threat from the standpoint of hemorrhage.

Leucocyte and Differential Count.—The white blood cell count did not contribute materially to the diagnoses or treatment.

There was a predominance of polymorphonuclear leucocytes over lymphocytes in most instances, appropriate for the age. In the presence of significant infection, the former generally increased unless the infection was of viral origin (e. g., chicken pox or rubella), when the proportion of granulocytes was often below average. Following active hemorrhage, the expected polymorphonuclear leucocytosis was seen.

Eosinophilia deserves special comment. As stated previously, there was a higher incidence of allergy in these cases, not only as manifested in the patients themselves but also in their family histories. In 34 of the patients there was an increase in eosinophiles to 5% or more. This is roughly a quarter of all the patients of both types. If this is divided, there were 20 with thrombopenia and 14 with normal platelet levels. There was a slight tendency for the eosinophilia to be of greater degree

4. These cases were reported recently: Epstein, R. D.; Lozner, E. L.; Cobbey, T. S. Jr., and Davidson, C. S.: Congenital Thrombocytopenic Purpura: Purpura Hemorrhagica in Pregnancy and in the Newborn, Am. J. Med. 9:44-56, 1950.

among those with thrombopenia, even if this form of the disease is not regarded as a hypersensitivity phenomenon. The average eosinophile percentages were 9% for the thrombopenic patients and only 6.5% for the patients with normal platelet counts. The highest eosinophile counts were found in the thrombopenic group, there being 6 patients with more than 10% eosinophiles. Two of these had 20% eosinophiles or more. There were no nonthrombopenic patients with counts above 10%.

The role of allergy has been discussed elsewhere, but these hematologic findings would seem to corroborate the clinical impressions regarding the important role of allergy in both types of purpura. Mere eosinophilia, to be sure, is admittedly not proof positive of an allergic diathesis. Nevertheless, taken with the family histories and allergic manifestations in these patients, the eosinophilia encountered may be related to hypersensitivity and is noteworthy as such.

Platelet Counts.—Platelet counts were important initially in helping to classify the patients as those with or those without thrombopenia. Thereafter they were of less importance. In following a given patient's response to a given form of therapy, however, the platelet count was of some help in confirming clinical improvement or failure to improve. Frequently there was a discrepancy between the clinical findings and the count. In these cases, the tourniquet test often more closely approximated the tendency to bruise or bleed. This was particularly true in patients who had been subjected to splenectomy. Although they bruised and bled less readily, their platelet counts often fell to or continued around 30,000 per cubic millimeter. Their tourniquet tests, however, remained relatively more normal. This finding, long noted by others, suggests a benefit to the vascular lesion out of proportion to that affecting the platelets. Although there were many exceptions, in general most patients began to experience significant bruising and bleeding when their platelet counts fell below 75,000 per cubic millimeter. As has been stated above, splenectomized patients frequently tolerated much lower counts with very few symptoms.

Bleeding and Clotting Times.—Among the thrombopenic patients, a large number had marked prolongation of the bleeding time, not uncommonly up to 30 minutes. But there was tremendous variation in this determination. With a definitely prolonged bleeding time, however, appreciable thrombopenia was the rule in this group of patients. There was certainly not the linear correlation one would expect if thrombopenia were the sole factor in determining the severity of the purpura.

In connection with the clotting time, its greatest usefulness is in ruling out hemophilia among male patients who complain of easy bruising. (Only 2 of the 96 thrombopenic patients had prolonged clotting times. These were for both 20 minutes. Both patients did well, their clotting times returned to normal, and their hemorrhagic tendency disappeared.)

Tourniquet Test.—As stated above, the platelet count occasionally showed poorer correlation with the patient's tendency to bruise and bleed than did the tourniquet test. This is a happy circumstance, as the latter is so much more easily performed than the former.

Tourniquet tests were positive for over 80% of the thrombopenic patients tested, whereas they were positive for only 10% of the nonthrombopenic patients. There was good correlation of this test with the clinical tendency to bruise and bleed. It

may be noteworthy that all thrombopenic patients characterized as having "strongly positive" tourniquet tests had platelet counts under 35,000 per cubic millimeter.

Urinalysis.—Like the patients with normal platelet counts, the majority of the thrombopenic patients showed no abnormalities in the urine whenever it was tested. Actually less than a quarter of the children with low-platelet counts (17 out of 96) showed even albuminuria. Only nine of these exhibited hematuria. In general, the reversibility of the renal lesion noted among the nonthrombopenic patients was also seen among those with thrombopenia.

Bone Marrow.—The few children in this series whose marrows were examined showed only moderate deviations from normal. Three examples will suffice. A 9-year-old girl with acute thrombopenic purpura had no evidence of infection. Her sternal marrow was aspirated on the fourth day after the onset of her nosebleeds. The marrow showed a total nucleated count that was average for our method (219,000 per cubic millimeter). The megakaryocytes were not increased in number (176 per cubic millimeter), nor were they decreased. The erythroid elements were increased (38%), doubtlessly stimulated by the blood loss. A differential count of the megakaryocytes revealed that about 25% of them showed vacuoles and decreased granules in the cytoplasm. Most of them were surrounded by platelets. Their nuclei showed increased lobulation.

A second example was an 8½-year-old boy who was admitted to the hospital because of hematuria for one day. Chicken pox had developed four days previously and two days previously the vesicles had become hemorrhagic. His sternal marrow was aspirated on the eighth day of his hematuria. The total nucleated count was slightly increased (321,000 per cubic millimeter) and the megakaryocytes were plentiful (198). The marrow was hyperplastic. The megakaryocytes showed increased vacuolization, lack of granulation, and small nonlobulated nuclei. A few had pyknotic nuclei. Most of them were noted to have some platelet formation. This child, too, made a rapid recovery, the hematuria ceasing after 10 days. He remains well.

A final example of bone marrow findings was that of a chronic resistant case of idiopathic thrombopenic purpura. The patient was a boy in whom easy bruising and nosebleed developed at the age of almost 8 years. He had had a splenectomy at a hospital in another city 18 months after onset without any benefit whatsoever to his spontaneous bruising or bleeding. A sternal marrow aspiration was done 3½ years after splenectomy. The marrow showed an increased cellularity and a definite increase in the number of megakaryocytes. There were many degenerated forms of these cells and only rare platelet formation. Most of the megakaryocytes were young; there was an occasional lobulated nucleus. The child, now 14, still bruises readily and has infrequent spontaneous nosebleed, but these symptoms are appreciably less severe than formerly and his general health is good.

Pathology of the Spleen.—As in the majority of reports concerning the histology of the spleen in thrombopenic purpura, our findings fail to reveal a consistent picture and disclose no pathologic lesion common to all spleens removed.

Twenty of the 23 splenectomized patients in this series had their spleens removed at the Children's Medical Center. The weight of the spleen of each patient was related to the average splenic weight for each age and the figure stated

in terms of per cent of average weight. A pattern was sought in relation to the clinical course, benefit from surgery, or the histology. None was found. The single exception was the patient with much the largest spleen which showed histologically the classical picture of fibrocongestive splenomegaly. He had suffered from a pneumococcal peritonitis at the age of 5 months and his spleen had been removed four years later because of low-platelet purpura.

Actually, if this case of fibrocongestive splenomegaly is omitted from the series, there was no significant variation between the average weights of the organs in these patients compared to normal. It is again noteworthy in this series, as in most others reported, that a number of patients suffering from the classical clinical picture of thrombopenic purpura are found to have spleens which are evidently normal from a morphologic standpoint.

Fatal Cases.—As stated earlier, most children with idiopathic thrombopenic purpura recover. Occasionally, however, complications may occur which can result in death. The physician, familiar with the hazards of thrombocytopenia and a free-bleeding tendency, will be better prepared to anticipate certain dangers and to treat them promptly should they develop.

In the series reported here there were four deaths. The first was an 8-year-old girl with chronic thrombopenic purpura in whom, over a course of 2½ years, nephritis and severe myocarditis developed. The second patient was a 3-year-old boy with a fulminating thrombopenic purpura of 24 hours' duration. He died within 48 hours and postmortem examination revealed no primary cause for the extensive hemorrhages into all organs, skin, and mucous membranes. His history, however, suggested that this illness was secondary to contact with a chemical present on the work clothes of the father who was employed dyeing sheepskins.

The third and fourth patients, 3 and 5 months old, respectively, had rapidly progressive fatal pneumonia associated with their thrombopenia, and extensive hemorrhages were found after death.

These examples emphasize the fact that thrombopenic purpura which generally runs a benign course with eventual recovery may occasionally develop fatal complications. Chief among these are (1) bleeding into vital organs such as the brain, the heart, or the kidneys and (2) superimposed infection. In this connection parents of active young children with thrombopenia must be alerted to the danger of mild trauma such as a bump on the head which may result in serious intracranial hemorrhage. Similarly, common infections generally considered mild may be complicated by hemorrhage and rapid spread of pathogenic organisms. Chicken pox, for example, in a child with antecedent thrombopenic purpura, has been known to result in a fatal septicemia. Prompt attention to even minor traumatic episodes and to early signs of infection is necessary to protect the child with thrombopenic purpura.

COMMENT

The nonthrombopenic patients of the anaphylactoid type present the lesser problem and can be considered more briefly. In our experience, these patients on the whole have done well, although their course is frequently punctuated by recurrent bouts of purpura which may be accompanied by joint pain, abdominal pain, melena, or hematuria. The patients in this group have recovered without residual

damage. Among the 44 nonthrombopenic patients, however, there were eight who presented clinical differences worthy of special comment. The noteworthy features of their disease were the longer course with exacerbations and remissions and the extensive renal involvement. They tended to show gross hematuria, nitrogen retention, and even hypertension. Abnormal signs and symptoms persisted in these patients for several months, and they did not return to completely normal health for as long as six months. All of them are now relatively well although two children have evidence of mild nephritis.

This group of eight patients has been of special interest. It is quite probable that they differ only in degree from the other nonthrombopenic patients. They obviously were suffering from a diffuse vascular disease. The relation of this disease to hypersensitivity in general remains obscure. The syndrome appears to be related clinically to such familiar entities as serum sickness, periarteritis nodosa, erythema nodosum, hemorrhagic nephritis, and rheumatic fever. More detailed and critical information is needed concerning the pathogenesis and lifetime course of this illness. The recent studies of Rich [5] and others have tended to support these varied diseases with an underlying pathology which has features that are more or less common to all of them. It is noteworthy that the one patient whose skin lesions were biopsied had an acute perivascular inflammation around the vessels of the derma. Although the disease of these children at various times may closely resemble rheumatic fever, erythema multiforme, periarteritis nodosa, or hemorrhagic nephritis, they cannot clearly be classified in any one of these categories. The ever-changing protean manifestations of their illness is perhaps its most striking feature. The varied signs and symptoms indicate a diffuse and widespread disease. Our patients in this group received only symptomatic treatment and they appear to have recovered.

In the patients with thrombopenic purpura, the situation is quite different. The doctor is confronted with a disease which may vary enormously in its severity, may be associated with serious hemorrhage, and in a few cases may eventually require surgery. The decisions as to when to transfuse or when to remove the spleen are important ones and require sound clinical judgment.

The experience of this clinic would indicate in the first place that thrombopenic purpura as it occurs in infants and children is frequently a relatively acute illness which progresses to spontaneous cure. Almost half our thrombopenic patients were "cured" within six weeks and about another seventh of the group became symptom-free within a year after the onset of their purpura. These facts clearly indicate that in children splenectomy should not be advised at the outset, especially if hemorrhage can be controlled.

The association of purpura of both types with respiratory infections has been striking. In a child with purpura, a conscientious effort should be made to identify as accurately as possible any infection present. This should include bacteriological cultures. In the presence of even low-grade tonsillitis, pharyngitis, or cervical adenitis, particularly when due to beta hemolytic streptococci, an adequate course of chemotherapy should be employed. If frank pus has accumulated, particularly

5. Rich, A. R.: Hypersensitivity in Disease with Especial Reference to Periarteritis Nodosa, Rheumatic Fever, Disseminated Lupus Erythematosus, and Rheumatoid Arthritis, Harvey Lect. (1946-1947) 42:106-147, 1947.

under pressure as in an acute otitis with a bulging eardrum, one must not neglect the cardinal surgical principle of adequate drainage. Even with fear of free bleeding, paracentesis should be performed, and the patient's general condition supported with transfusion and appropriate chemotherapy.

True neonatal thrombopenic purpura proved by adequate blood studies occurred in only one patient in this series, though several others reported bruising since birth. This child was interesting in that he was born of a mother who had chronic idiopathic thrombopenic purpura for which she had been splenectomized before her marriage. Our patient had marked thrombopenia at birth, but his platelet count gradually rose to 134,000 per cubic millimeter when he was 11 weeks old, and he has remained cured. His two siblings, both males, have had similar courses. All were treated only by transfusion. The course of these children would suggest a humoral factor from the mother which depressed platelet production during gestation. Regardless of the pathogenesis, the practical lesson learned from these children is the importance of frequent transfusion during the neonatal period to tide them over until such time as possible platelet destruction subsides and their own platelet production becomes adequate. Without transfusion the prognosis for these patients is poor, judging from the literature.

In connection with the role of infection in a large number of our patients, there are several possibilities. It may well be that increased capillary permeability or toxic suppression of the megakaryocytes has resulted from the direct action of a toxin elaborated by bacteria. This would appear to be the mechanism of the capillary damage in overwhelming scarlet fever, and it may apply to all cases, though we do not believe so. Another explanation may involve hypersensitivity. We have found an increased incidence of personal and family histories of allergy among our patients. Furthermore, certain time relations between infections and purpura make a sensitizing interval seem like a plausible explanation. The "end organ" affected by such a hypersensitive reaction would be the megakaryocyte, the platelet, the capillary wall, or a combination of these.

In most instances this is a self-limited abnormality and recovery is the rule. Splenectomy may become necessary in a small percentage of cases, the patients chiefly consisting of young active boys whose bleeding episodes recur very frequently and in whom the control of everyday trauma is difficult, girls approaching the menarche when frequent exsanguinating uterine hemorrhage occurs, and patients with acute severe purpuras when no ordinary treatment has carried them through the dangerous bleeding period. This whole group does not amount to more than 10% of the patients whom we have seen.

SUMMARY

We have reviewed cases of 140 infants and children with purpura treated in this clinic in the 12 years, 1936 to 1947 inclusive. The ratio of thrombopenic to nonthrombopenic cases was approximately 2:1.

Infection appeared to play a prominent role in these cases. Approximately two-thirds of the patients had the onset of their purpura concomitant with or soon after the onset of an acute infection. The majority of these were respiratory infections, there being 12 exceptions, 6 of which were acute exanthemata.

Positive family histories for allergy were found in more than a quarter (28.6%) of the patients and personal manifestations of allergy were noted in a fifth (19.3%) of the patients themselves.

The combination of a high incidence of demonstrable infection in these patients together with an increased incidence of frank allergic manifestations is compatible with the hypothesis that an appreciable number of cases of both types of purpura may represent a reaction to a bacterial antigen in a hypersensitive patient, resulting in damage to the platelets, the capillaries, or the megakaryocytes, singly or in combination.

Nonthrombopenic purpura in infants and children is almost invariably a benign, though sometimes protracted and self-limited, disease. With symptomatic treatment these patients generally recover without residuals.

A few patients with nonthrombopenic purpura have shown illnesses lasting three to six months characterized by marked kidney involvement, hypertension, and nitrogen retention. These patients, too, have recovered completely in the series reported here.

Thrombopenic purpura in infants and children is often an acute self-limited illness, which may be associated with antecedent infection.

IMMATURITY OF SINGLE LIVE BIRTHS ACCORDING TO WEIGHT, WITH PARTICULAR REFERENCE TO RACE

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THERE has been considerable conjecture in Hawaii and elsewhere as to whether the same weight standard for immature births may be applicable to all races. It has been quite generally accepted that white babies weighing 2,500 gm. or less at birth are immature. But does this weight limit apply equally well for babies of other than Caucasian blood; does it apply for Chinese, Japanese, and Filipino babies whose mothers are generally small of stature?

The population of Hawaii, 86% of whom are U. S. citizens, is divided into six categories and is predominately nonwhite (Table 1).

TABLE 1.—*Racial Origin of Population of Hawaii*

Race of Origin	Population July 1, 1951	Per Cent
All races	472,602	100.0
Hawaiian and Part-Hawaiian	90,683	19.2
Caucasian	78,477	16.6
Chinese	33,499	7.1
Japanese	186,609	39.5
Filipino	61,185	12.9
Other	22,149	4.7

The Chinese, Japanese, and Filipinos, all of whom are generally physically smaller than the Caucasians and Hawaiians and usually smaller than the Part-Hawaiians,[1] comprise 60% of the total population.

Of a total of 14,182 single live births in 1951, 51% were classified as either Chinese, Japanese, or Filipino by race of origin of the mother, and over a third were Japanese.

If the 2,500 gm. upper weight limit of immaturity is not applicable to peoples of small build, it is obvious that the picture of immaturity in Hawaii would then be considerably biased by the sheer preponderance of babies born to mothers who are characteristically of small stature.

Chief of the Bureau of Health Statistics (Mr. Taff) and President of the Board of Health (Dr. Wilbar), Health Department of Territory of Hawaii.

1. Part-Hawaiians are persons with any amount of Hawaiian blood and are so classified because of certain personal and property rights to which people of Hawaiian ancestry are legally entitled.

The following paragraphs therefore are an attempt to determine the extent of immature births among the various ethnic groups in Hawaii, and to determine whether 2,500 gm. as an upper limit of immaturity can be used as an equitable standard for each of the several races.

All single live births of known birth weights which occurred in Hawaii during 1951 to resident mothers are included in the study. (Only 49 births had to be excluded because of unknown weight.) Ninety-seven per cent of these births occurred in hospitals, and only 2% were delivered by nonmedical attendants. Only deaths of the above births which occurred within less than 29 days after delivery are included, and no death had to be excluded because the birth had not been reported. All deaths occurred in hospitals.

Birth registration in Hawaii is 99.9% complete, according to the 1950 birth registration test, and indications are that death reporting is equally good.

SEX AND RACE

Of 14,182 single live births of known birth weight which occurred during 1951 there were 1,036 (7.3%) classified as immature by weight (2,500 gm. or less).

TABLE 2.—*Per Cent of Babies Born Immature*

Race	Both Sexes	Male	Female
Japanese	6.0	6.3	5.8
Caucasian	6.1	5.5	6.7
Chinese	7.3	6.7	7.9
All races	7.3	7.1	7.5
Hawaiian	7.9	8.7	7.1
Filipino	12.1	10.4	13.9

TABLE 3.—*Ratio of Males per One Hundred Females by Race*

Race	Immature	Mature
Japanese	117	108
Caucasian	92	113
Chinese	92	108
All races	100	102
Hawaiian	122	96
Filipino	82	106

By sex, 7.1% of the male babies and 7.5% of the female babies were born immature; the difference is not significant. However, a breakdown of these figures by race and sex shows some highly interesting variations (Table 2).

Among mature infants of all races there were slightly more males than females (102 males/100 females). By race there was a variation of from 96 males/100 females among Hawaiians to 113/100 among the Caucasians. The Japanese, Chinese, and Filipinos had about the same sex ratios—108, 108, and 106, respectively (Table 3).

The sex ratio among immature babies was, however, considerably different and showed wide variations. For all races the sex ratio was 100 males/100 females, about the same as for mature babies of all races. The Filipinos had the lowest ratio (82 males/100 females) and the Hawaiians the highest (122/100) with the Japanese running a close second (117 males/100 females). The Chinese and Caucasians had the same sex ratio (92).

AGE OF MOTHER

On an average, more than 1 out of 10 babies born to mothers under the age of 20 were immature. Mothers between 20 and 29 had fewer immature infants (7.0%), and those between 30 and 39 had the least (6.4%). The odds that mothers in their forties will have immature babies are nearly the same as for mothers under 20 (1 in 10). Considerable variation, however, occurred among mothers of different races (Table 4).

Caucasian and Japanese women were exceptions to greater likelihood of having immature babies in their forties. Furthermore, Japanese women experienced only slight variations in risk from one age group to another. Filipino women ran a much higher risk of having immature babies at all ages.

TABLE 4.—*Per Cent of Immature Babies by Age and Race of Mother*

Race	All Ages	Under 20	20-29	30-39	40-49	50 and Over *
All races	7.3	11.7	7.0	6.4	10.9	50.0
Hawaiian	7.9	10.5	7.0	8.3	11.9	50.0
Caucasian	6.1	7.1	6.1	5.9	3.4	....
Chinese	7.3	12.5	6.5	6.9	23.5	50.0
Japanese	6.0	6.1	6.1	5.8	6.6	....
Filipino	12.1	19.8	10.9	7.3	20.8	....

* Total of 4 births of which 2 were immature.

TABLE 5.—*Per Cent of Immature Babies by Race of Mother and Parity*

Race	Total	1	2	3	4	5	6	7	8	9
All races	7.3	8.7	6.9	6.1	6.7	6.7	7.5	7.1	8.3	6.4
Hawaiian	7.9	10.3	7.6	7.1	7.9	5.8	7.7	6.7	4.7	5.9
Caucasian	6.1	7.4	6.1	4.6	5.6	1.8	3.8	18.2	25.0	0
Chinese	7.3	9.2	5.8	5.1	5.7	17.0	10.0	0	...	0
Japanese	6.0	6.7	6.1	5.3	4.9	5.3	9.9	5.3	2.9	5.0
Filipino	12.1	17.6	10.6	9.9	11.2	10.5	6.7	8.5	16.7	8.8

PARITY

Among all of the races, except for the first and the eighth child, parity appeared to make no great difference in the percentage of immature births. However, there was so much variation beyond the fourth pregnancy by race of mother that one might question the validity of the data (Table 5).

Fifth-born infants were most prone to immaturity among Chinese mothers; sixth-born among Chinese and Japanese; seventh-born among Caucasian; eighth-born among Caucasian, and ninth-born and over among Filipino mothers. The Filipino rates were high for all births except the sixth.

DEATH RATES OF IMMATURE BABIES

Of every 100 immature babies 15 died within the first 28 days after birth, with the males dying at a rate 50% higher than the females.

By race the percentage dying within the first 28 days ranged from a low of 11.9 for Chinese to a high of 16.0 for Japanese. The Filipino rate of 14.4% was the second lowest.

For the weight group 2,001 to 2,500 gm. only 1 baby for each 30 live births failed to survive the first 28 days. The mortality rate for the male babies was over twice as high as that for the females.

COMPARISON OF THE MORTALITY RATES OF IMMATURE AND MATURE INFANTS

The neonatal death rate among immature babies was almost 30 times as high as that for mature babies. By age of mother the death rates were lowest for immature babies born to mothers in their twenties. The lowest death rates for mature babies were among those born to mothers in their teens. The highest death rates for both mature and immature babies occurred when the mothers were in their forties.

The neonatal death rates for immature and mature single live births varied considerably by race of mother (Table 6). Peculiarly, the Filipinos, with the

TABLE 6.—*Neonatal Death Rates for Immature and Mature Single Live Births*

Race	Immature	Mature
Chinese	119.4	4.7
Filipino	143.7	10.3
Hawaiian	150.0	5.5
All races	152.2	5.3
Caucasian	152.3	3.0
Japanese	160.4	5.7

TABLE 7.—*Per Cent of Total Births in Weight Groups by Race of Mother*

Race	Total	-500	-1000	-1500	-2000	-2500
All races	100.3	1.4	4.6	6.0	14.6	73.9
Hawaiian	100.2	0.4	7.1	6.3	14.6	71.8
Caucasian	100.1	1.5	4.1	5.6	14.8	74.1
Chinese	100.0	1.5	1.5	4.5	14.8	77.7
Japanese	100.2	2.4	4.4	5.8	14.4	73.2
Filipino	100.0	0	3.4	6.9	13.2	76.5

second lowest immature death rate, had by far the highest death rate for mature babies.

COMMENT

During 1951 in Hawaii Filipino women had premature babies at a rate 78% higher than women of all other races. By sex, Filipino women have male immature babies at a rate 54% higher than women of all other races and female immature babies at a rate 105% higher. One possible explanation of this could be that 2,500 gm. is too high as a weight criterion for the upper limit of immaturity for Filipinos, who are generally small in stature.

If such an assumption be true, it would seem to follow that proportionately the largest number of immature Filipino infants would fall in the weight group 2,001 to 2,500 gm., for if the standard is too high the percentage of babies in this group would be inconsistent with the percentage of babies of other racial extractions in this same group. The per cent of total births in each weight group by race of mother is shown in Table 7.

The Filipino women had a high percentage of babies born in the 2,001 to 2,500 gm. weight group, but not the highest. Moreover, the difference between the percentage for Filipinos (76.5) and that for all other races (72.2) is not significant ($X^2 = 1.17$). The Filipinos had the highest percentage of babies in the 1,001 to 1,500 gm. group, but this could hardly be accredited to misclassification. The percentage of male Filipino babies in the weight group 2,001 to 2,500 gm. (71.8) was not significantly different ($X^2 = 0.61$) from the percentage of male babies of all other races in this weight group (71.4). Nor was the difference between the percentage of female Filipino babies (80.2) and non-Filipino female babies (74.9) significant ($X^2 = 1.13$).

The Chinese had the largest percentage of immature babies in the 2,001 to 2,500 gm. weight group, but the numbers are small and the difference from the per cent for "All Races" is not significant. The Japanese had the second lowest

TABLE 8.—*Death Rates* of Babies Weighing 2,001 to 2,500 Gm.*

Race	Total	Male	Female
All races	3.3	4.9	1.8
Hawaiian	2.3	4.2	0
Caucasian	4.1	7.8	1.2
Chinese	3.8	3.8	3.8
Japanese	2.3	3.6	1.0
Filipino	3.8	5.4	2.6

* Number deaths per 100 births.

TABLE 9.—*Percentage of Immature Births According to Race*

Race	Per Cent Immature
Japanese	6.0
Caucasian	6.1
All races	7.3
Chinese	7.4
Hawaiian	7.7
Filipino	10.9

percentage of immature birth. It would not seem, therefore, that small stature necessarily places proportionately more babies in the weight group 2,001 to 2,500 gm.

Also, under the assumption that 2,500 gm. is too high an upper limit of immaturity among Filipinos, if a considerable number of Filipino infants had been incorrectly classed as immature when actually they were mature, it would seem to follow that the death rates of these incorrectly classified babies would be lower than those of other races who are correctly classified, for immature babies die at a rate about 30 times as high as mature babies (Table 8).

As shown, the facts do not bear this assumption. The death rate for immature Filipino babies born in the 2,001 to 2,500 gm. weight class was higher than that for all races together and tied for second highest with the Chinese. By sex the Filipino mortality rates were also second highest, exceeded only by the Caucasian rate for males and the Chinese for females.

Part of the answer as to why the Filipinos have a high percentage of immature births, although not the entire answer by any means, is found in the age distribution of the mothers. Nearly 17% of the Filipino mothers were under age 20 whereas only 9% of mothers of all races were under age 20. The percentage of immature babies of Filipino mothers under 20 years of age was 19.8; for all mothers in this age group 11.7. This high proportion of mothers of an age when immaturity occurs in a high proportion of births obviously weighted the overall percentage of immature births. To eliminate the effect of the varying age composition of the several races the standardized rates (Table 9) were computed. Even though the standardization lowered the Filipino immaturity percentage, it is still significantly high.

CONCLUSIONS

Filipino mothers had proportionately more immature babies by weight than mothers of any other race, and even when the rates are standardized for age, the Filipino rates were still significantly high.

The proportion of Filipino infants in the weight group 2,001 to 2,500 gm. was not significantly higher than that of other racial backgrounds.

The death rate of Filipino babies in the weight group 2,001 to 2,500 gm. was exceeded only by Caucasian babies and was considerably higher than babies of all of the other races except Chinese, for which it was identical.

If 2,500 gm. as an upper limit of immaturity is too high for Filipino babies, it would seem to follow that the proportion of babies weighing 2,001 to 2,500 gm. would have been higher than other races. It would also seem that the death rate for Filipino babies in this weight class would have been low. As shown in the two preceding paragraphs, neither of these qualifications has been satisfied. It therefore appears that 2,500 gm. is not too high an upper limit for the determination of immature Filipino babies.

Furthermore, if 2,500 gm. were too high a standard for Filipino babies it would seem that it might also be too high for the Chinese and Japanese, as these races also tend to be of comparatively small stature. The Japanese had the lowest percentage of immature births and the Chinese percentage was the same as for all races. Conversely, the Hawaiians who are of average to large stature had the second highest per cent of immature babies.

From the above it appears that 2,500 gm. was an acceptable upper limit of immaturity for babies born to all racial groups living in Hawaii in 1951.

PRENATAL CLOSURE OF THE INTERATRIAL FORAMEN

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THE ABSENCE of an interatrial communication before birth causes distortions in cardiac development which render the heart incapable of proper function after birth. Patten [1] has called attention to the fact that the foramen ovale normally transmits at least half of the blood that enters the left side of the fetal heart. Premature closure of the foramen, therefore, deprives the left atrium and ventricle of all blood from the systemic and placental circulations. Only the pulmonary circulation, which in the fetus is of relatively small quantity, empties into the left atrium. Since this is not sufficient to bring about normal expansion and muscular development of the left-sided chambers, they become hypoplastic, whereas the right-sided chambers tend to become distended and hypertrophied. The right ventricle during fetal life must assume the entire burden of pumping blood through the systemic circulation by way of the ductus arteriosus. These conditions may be tolerated prenatally, but the changes in the circulation which occur shortly after birth introduce complications that are incompatible with postnatal life. The sudden increase in the volume of blood delivered from the lungs to the left side of the heart cannot be accommodated by the underdeveloped left atrium and ventricle. The ensuing course of events, in more or less rapid order, is venous congestion of the lungs, cyanosis, dyspnea, and death.

Prenatal closure of the interatrial foramen has been recorded only rarely. Lehman [2] found five cases [3] reported in the medical literature between 1715 and

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1. Patten, B. M.: Developmental Defects at the Foramen Ovale, Am. J. Path. **14**:135, 1938.

2. Lehman, E.: Congenital Atresia of the Foramen Ovale, Am. J. Dis. Child. **33**:585, 1927.

3. Vieussens, R.: Traité nouveau de la structure et des causes du mouvement natural du coeur, Ed. 1, Toulouse, J. Guillemette, 1715, p. 35, cited by Corvisart, J. N.: Essai sur les maladies et les lésions organiques du coeur, Ed. 3, Paris, Méquignon-Marvis, 1818, p. 315. Smith, E.: Premature Occlusion of the Foramen Ovale: Large Pulmonary Artery and Duct, and Contracted Left Heart, Tr. Path. Soc. London **1**:52, 1846. Vernon, H. H.: Two Cases of Malformations of the Heart, Med.-Chir. Tr. London **39**:297, 1856. Tait, L.: A Case of General Dropsy in a Fœtus, Tr. Obst. Soc. London **17**:307, 1876. Osler, W.: Cases of Cardiac Abnormalities, Montreal Gen. Hosp. Rep. **1**:177, 1880.

1927, and he added one case himself. He omitted a probable case reported by McIntosh [4] in 1926. Since that time eight additional instances [5] have been described. Thus, including the two cases to be presented here, the condition has been observed a total of only 17 times. It is suspected, however, that the actual incidence is somewhat higher than this figure indicates. The basic defect, namely, absence of an interatrial communication, is one that may be overlooked since it can occur in an interatrial wall that appears normal on superficial examination. The associated aplasia of the left atrium and ventricle is not in itself a reliable diagnostic feature, since it is subject to considerable variation in degree and is known also to occur in association with other cardiac malformations. Furthermore, since prenatal closure of the interatrial foramen predisposes to death early in the postnatal period, the defect must be sought in stillborn infants or in those dying within a few hours or days after birth. Only in recent years has careful postmortem examination of neonatal infants been extensively practiced. Perhaps this accounts for the fact that the number of cases of prenatally-closed foramina encountered in the past 20 years exceeds that recorded in all of previous medical history.

REPORT OF CASES

CASE 1.—The only clinical information available was the statement that the infant lived 36 minutes after delivery. The authors were told that there was no record of untoward events during pregnancy.

Summary of Autopsy Record.—The infant was a well-developed white boy who exhibited cyanosis of the face, neck, and nail beds, but no other external findings of note. When the thoracic and abdominal cavities were opened, it was found that the left half of the diaphragm was absent, and the left side of the thoracic cavity contained the stomach, spleen, left lobe of the liver, and part of the small intestine. The right half of the diaphragm also had a muscular defect along its posterolateral border, but the defect was covered by serous membranes, and no herniation had occurred here. The colon was incompletely rotated, and the cecum and appendix were found in the left upper quadrant. The testes were within the abdominal cavity at the midlumbar level.

The thoracic viscera were shifted to the right side. The left lung was very small (2.5 cm. by 1.5 cm. by 0.8 cm.) but had apparently undergone some aerations, since it floated when placed in water. The right lung was about normal in size and appearance. The heart (as described in the original autopsy record) was a small two-chambered organ with a single arterial trunk leading from the ventricle. This trunk gave off the pulmonary arteries and appeared also to give rise to a single large artery which in turn gave rise to branches that corresponded to the branches of the arch of the aorta. The main trunk then continued downward in the usual relationships of the descending aorta. The superior and inferior venae cavae and minute pulmonary veins appeared to enter a common atrial chamber.

4. McIntosh, C. A.: Cor Biatriatum Triloculare, Am. Heart J. **1**:735, 1926.

5. (*a*) Patten.[1] (*b*) Bellet, S., and Gouley, B. A.: Congenital Heart Disease with Multiple Cardiac Anomalies, Am. J. M. Sc. **183**:458, 1932. (*c*) Read, W. T., Jr., and Krumbhaar, E. B.: Eight Cases of Congenital Heart Disease, M. Clin. North America **16**:229, 1932. (*d*) Benner, M. C.: Premature Closure of the Foramen Ovale, Am. Heart J. **17**:437, 1939. (*e*) Kreutzer, R., and Visillac, V. O.: Cierre precoz del foramen oval, Semana méd. **1**:720, 1942. (*f*) Hyman, M. A.: Absence of the Left Cardiac Ventricle with Aplasia of the Aortic Orifice and Hypoplasia of the Aorta, Arch. Path. **42**:590, 1946. (*g*) Edwards, J. E., and DuShane, J. W.: Thoracic Venous Anomalies: I. Vascular Connection of Left Atrium and Left Innominate Vein (Levoatriocardinal Vein) Associated with Mitral Atresia and Premature Closure of the Foramen Ovale: II. Pulmonary Veins Draining Wholly into the Ductus Venosus, Arch. Path. **49**:517, 1950.

Detailed Study of the Heart.—Since a detailed study of this unusual heart was not attempted at the time of autopsy, the authors present here an anatomical description of the preserved specimen. It was of small size, weighing 10.5 gm. as compared with the average weight of 18 to 20 gm. of similarly preserved normal hearts from infants of comparable size. Externally only two chambers were apparent (Fig. 1). No interventricular sulci were visible, and the arrangement of blood vessels on the ventricular wall was such as to afford little indication of internal partitioning. The atrial portion of the heart had the external features typical of a right atrium except that it appeared to have two auricular appendages projecting toward the left side, one lying anterior and the other posterior to the large arterial trunk which emerged from the ventricle.

The heart was opened by a single continuous incision extending from the inferior vena cava downward through the posterior ventricular wall, across the apex, upward along the anterior ventricular wall, and out the large arterial trunk. Internal structures indicated the two larger chambers thus exposed to be right atrium and ventricle. Close inspection of the incised surfaces revealed a slit-like cleft within the posterior wall of both of these chambers. When the wall

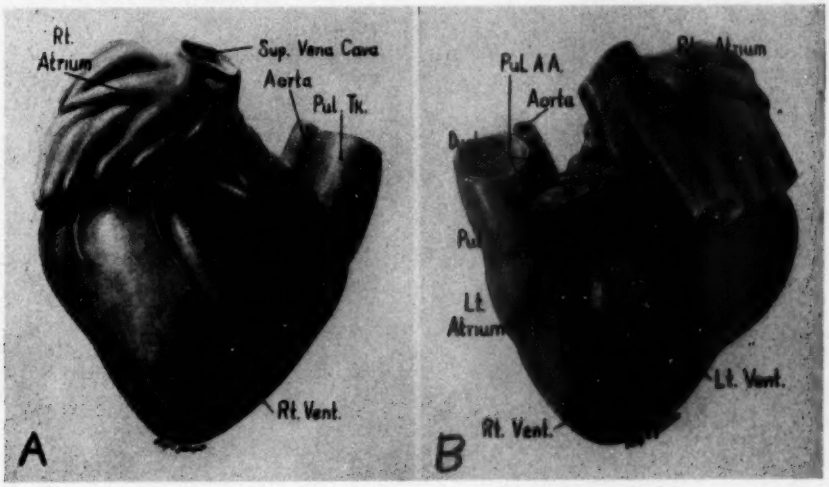

Fig. 1 (Case 1).—*A*, anterior view. *B*, posterior view.

was spread apart in a manner which exposed the interior of the clefts, they were identified as the left atrium and ventricle since they communicated with each other through a structurally well-formed but proportionately small mitral valve (Fig. 2*A*). The left ventricle possessed scarcely more than a potential lumen, but did contain papillary muscles, chordae tendineae, and mitral valve leaflets that were properly formed but miniature in size. There was no trabecular arrangement of the muscle on the internal surface. The interventricular septum was complete.

A probe inserted behind the aortic leaflet of the mitral valve passed out of the chamber and emerged from an inconspicuous vessel that adhered to the wall of the large arterial trunk, which was now recognized as the pulmonary trunk. The small vessel proved to be the ascending aorta after the pericardium and adventitial tissue that bound it to the pulmonary trunk were removed. The right and left coronary arteries could be traced from the coronary sulcus to their origin at the base of the aorta. When the aorta was opened, its valve was found to consist of only two cusps of about equal size, one anterior and the other posterior in position. Both coronary arteries originated in the sinus enclosed by the anterior cusp. The remainder of the ascending aorta was uniformly small and collapsed and would admit a probe no larger than 2 mm. in diameter.

The left atrium, when viewed externally, had much the appearance of an accessory auricular appendage which projected from the right atrium toward the left side and posterior to the aorta and pulmonary trunk (Fig. 1*A*). After it was opened, the chamber was estimated to have a

capacity of about 2 cc. The outer wall was of nearly uniform thickness, approximately 1 mm., and showed none of the characteristic pectinate muscles. The septal wall was also smooth and lacking of distinctive markings. No valvula was recognizable. There were only two openings through the walls of the left atrium. The left atrioventricular orifice with its small but well-formed valve has already been mentioned. The other orifice was a single small pulmonary vein which entered at the center of the posterior wall. This vessel was only large enough to admit a 1.5 mm. probe.

The right atrium was approximately normal in size and structure, except in the region of the atrial septum. The septal wall was much reduced in size and the distance between the orifices of the superior and inferior venae cavae was only about half that usually seen. No fossa ovalis or limbus fossa ovalis was found (Fig. 2*B*), and the only surface markings were a few randomly-arranged ridges and depressions. Careful exploration of these depressions with a small probe revealed them to be blind pits or grooves with no opening into the left atrium.

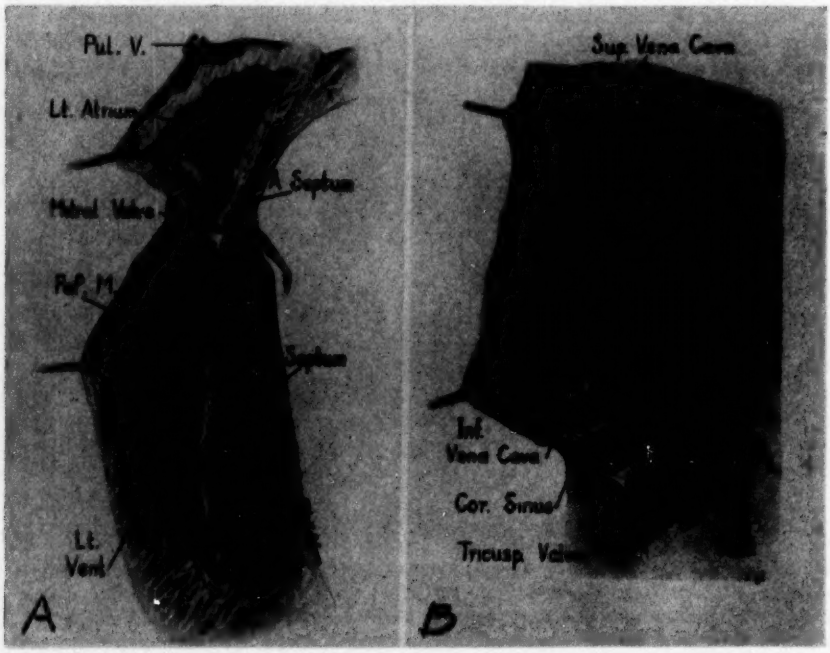

Fig. 2 (Case 1).—*A*, section through the posterior wall of the heart, showing the left atrium and ventricle as scarcely more than slits in the wall of the right atrium and ventricle. *B*, view of the interatrial septum from the right side. Note the absence of the limbus and the fossa ovalis.

The right ventricle was abnormal only in that its shape was distorted (Fig. 1) owing to the failure of concomitant development of the left ventricle. All of the apex and the greater part of the ventricular portion of the entire heart was composed of the right ventricular chamber. Internal structure, aside from the distortion of relationships, was essentially normal. Neither the thickness of the wall nor the degree of development of trabeculae carneae indicated any appreciable hypertrophy. Arising from the left superior aspect of the chamber the dilated pulmonary trunk arched backward, gave off the two pulmonary arteries, and then continued in scarcely diminished size as the ductus arteriosus. The right pulmonary artery measured 3 mm. in diameter, the left only 1.5 mm. At the point where the ductus became continuous with the descending aorta a large arterial branch appeared to arise and pass in a cephalic direction. From it arose vessels which were identified as the innominate, left common carotid, and left subclavian arteries and a much smaller vessel which arched toward the right side. This smaller

vessel was of the same caliber (2 mm. in diameter) as that which arose from the left ventricle and which was identified as the ascending aorta. When the cut ends of these two vessels were approximated, it became apparent that they represented the arch and ascending part of the aorta which had been severed when the heart was removed. Thus the arch of the aorta was established to be present and patent throughout its course, but its lumen was so diminished that it could not have delivered more than a small fraction of the blood ordinarily carried to the descending aorta and to the three large arteries that normally arise from the arch. All of the latter vessels must have received the greater part of their blood through the enlarged ductus arteriosus (Fig. 3).

Comment.—This specimen exhibits perhaps a more extreme degree of hypoplasia in the left-sided chambers than any yet observed, except the one described

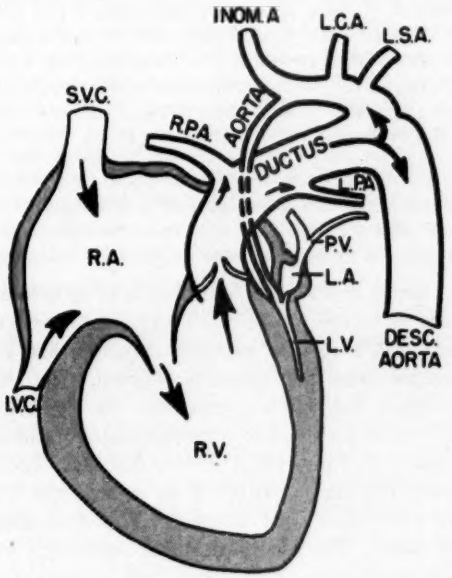

Fig. 3 (Case 1).—Schematic representation of the cardiac circulation.

by Hyman [5f] which had complete aplasia of the left ventricle. During fetal life no more than the merest trickle of blood could have passed through the left atrium and ventricle. The only blood entering the atrium came through a solitary small pulmonary vein. Although the flow of blood to the heart from the lungs is normally small during fetal life, it seems unlikely that a vessel as small as the one observed carried the entire pulmonary drainage. Unfortunately, the probability of accessory pulmonary drainage was overlooked at the time of autopsy, and from the material available for detailed study by the authors it was impossible to ascertain whether any pulmonary veins had emptied elsewhere than into the left atrium. At least one previous case of prenatal atresia of the interatrial foramen is known to have been associated with aberrant pulmonary veins.[5g]

Case 2.—A Negro infant boy, born prematurely after a gestation period of 246 days, weighed 2,100 gm. (4 lb. 10 oz.) and measured 43 cm. (17.2 in.) in length. He failed to breathe prop-

erly, became deeply cyanotic, and died four hours after birth. An apical systolic murmur had been heard, but otherwise the physical examination revealed no significant abnormalities. The mother's health had been good throughout her pregnancy.

Summary of Autopsy Record (Pathologist, Dr. Ralph Johansmann).—The infant was well developed and had no externally visible abnormalities. The abdominal and pericardial cavities each contained only a few cubic centimeters of clear serous fluid, and the pleural surfaces were moist. The brain and all thoracic and abdominal viscera except the heart and lungs were normal.

The heart weighed 15 gm. There was marked dilatation of the right atrium and moderate dilatation of the right ventricle. All heart valves were structurally normal, but the aortic valve was abnormally small, measuring only 12 mm. in circumference as compared with 20 mm. for the pulmonary valve. The walls of the two ventricles were of equal thickness (4 mm.) although the right ventricle was of somewhat larger capacity. The interatrial septum was distinctly abnormal. Both of the septal components were present, but they appeared to have fused completely, thus obliterating the foramen ovale and transforming it into a fossa ovalis. With the limbus as its margin, the fossa ovalis bulged deeply into the left atrium as a thin membrane shaped somewhat like an expanded parachute. The diameter of the sacculated membrane was 10 mm., and its depth was 6 mm. Further exploration of the distorted fossa revealed a small slit-like aperture 2 mm. in length in its inferior margin. It is improbable, however, that this aperture could have functioned as a foramen, since the septal components at this point were fused in such manner as to prevent its opening. Except the ductus arteriosus, which was moderately increased in diameter, the remainder of the heart and great vessels were normal.

The lungs had the usual configuration, but appeared to be abnormally voluminous considering the fact that they were almost airless. This solid tissue was not increased in friability, but appeared to be congested. No preparations were available for microscopic study.

Comment.—The family history of this patient is of considerable interest because of the high frequency of murmurs and other cardiac abnormalities in five siblings. The oldest, 11 years, had a systolic murmur along the left sternal border but a normal cardiac roentgenogram and electrocardiogram. The second child, 7 years of age, had no murmurs, but in roentgenograms the heart measured 11 cm. in width in a chest 19.5 cm. in width. The electrocardiogram showed diphasic P waves in Leads I and II and a P-R interval of 0.18 to 0.20 sec. The third child, 6 years of age, had a transient murmur, probably of no significance. Her heart, however, measured 10 cm. in width in a chest 17 cm. wide, and an abnormal convexity of the left margin was noted. The electrocardiogram showed a P-R interval of 0.18 second and some diphasic P waves. The fourth child, 4 years of age, had a transient murmur, and a heart measuring 9.5 cm. in a chest of 17.7 cm. in width. The electrocardiogram was normal. The fifth sibling, 2 years old, had had a murmur at birth which was no longer audible. By roentgenogram the heart measured 8.2 cm. in width in a chest of 15.5 cm. The electrocardiogram was normal.

COMMENT

The 17 cases of prenatal closure of the interatrial foramen summarized in the table are divisible into two groups: those in which closure was complete before birth, and those in which a small but functionally inadequate communication persisted. In other words, the foramen usually seen at the time of birth may, on rare occasion, be either atretic or stenotic. The degree of abnormal closure, however, appears to have made little difference in the viability of this group of infants. None lived for more than five weeks and only 5 of the 17 lived longer than one day. Only one of the latter five belonged to the group exhibiting even a "probe patency" of the foramen at the time of autopsy. The only known factor which might have contributed to the prolongation of life beyond a few days was the existence of an

outlet for the vascular impasse which tended to develop in the left side of the heart, as a result of the small size of the aorta and the hypoplasia in the left-sided chambers. Such an outlet was observed in two of the cases. The hearts described by McIntosh [4] and by Edwards and DuShane [5g] both possessed a very unusual vein which connected the left atrium with the superior vena cava or one of its major tributaries. The patient of Edwards and DuShane had in addition a right pulmonary vein emptying into the superior vena cava and a defect in the ventricular septum. Although not serving greatly to improve the circulatory efficiency of the patients, these abnormalities did relieve somewhat the vascular congestion which tended to develop in the lungs and the left chambers of the heart.

The cause of death in the live-born infants appears to have been related to the venous congestion in the lungs. Although overt signs of congestion were not reported at autopsy in all instances, the prevalence of respiratory difficulty and cyanosis during life (Table) suggests that acute congestion was a regular feature. The frequent lack of pathological changes in the lungs was probably related to the short duration of life. Generalized edema, possibly reflecting right heart failure, was noted in five patients, the majority of whom were stillborn infants or those dying within a few minutes after birth. Whatever the immediate cause of death in these cases, it seems evident that prenatal reduction of the interatrial foramen to a diameter less than approximately 5 mm. is incompatible with long-continued postnatal life, and occasionally may result in death during the late fetal period. The exact degree of stenosis that may be tolerated is a moot question.

Although the prognosis of this condition is apparently hopeless, it is nevertheless interesting to consider the possibilities of diagnosis before death. The typical patient became cyanotic soon after birth, developed respiratory difficulties, and died within a few hours or days. Further clinical data were extremely meager. In roentgenograms of the patient described by McIntosh [4] a moderately-enlarged heart was observed, and the electrocardiogram showed a sinus tachycardia and marked right ventricular preponderance. Roentgenologic examination of the patient of Edwards and DuShane [5g] demonstrated cardiac enlargement and pulmonary congestion. Generalized enlargement of the right side of the heart has been a common pathological finding (Table), but no typical configuration of the heart has been demonstrated roentgenographically.

The clinical manifestations of the disorder in infants living for longer than a few hours have consisted chiefly of cyanosis, dyspnea, cardiac enlargement, pulmonary congestion, and circulatory failure. Confronted with such a group of symptoms in a newly-born infant, one may quickly eliminate the tetralogy of Fallot, tricuspid stenosis, and isolated pulmonary stenosis because these disorders are usually associated with normal-sized hearts, loud rough murmurs, and pulmonary undercirculation. Other cardiac malformations are more difficult to differentiate. Transposition of the great vessels, abnormal patency of the atrial septum, two-chambered or three-chambered hearts, and gross atresia of the aortic or mitral valves (Gunn and Miale [6]) may produce symptoms somewhat similar to those of premature atrial closure. If the patients lived long enough, angiocardiography might aid in the differential diagnosis of these conditions. Still another group of cardiac conditions of infancy which likewise exhibit enlargement of the heart and

6. Gunn, J. A., and Miale, J. B.: Aortic Atresia, Mitral Stenosis, Hypoplasia of Left Ventricle and Other Cardiac Anomalies in the Newborn, Arch. Path. **50**:464, 1950.

TABLE 1.—*Summary of Reported Cases of Prenatal Closure of the Interatrial Foramen*

Reference	Duration of Life	Condition of Heart					Clinical Data			
		Degree of Closure of Interatrial Foramen	Hypoplasia of Left-sided Chambers	Enlargement of Right-sided Chambers	Aorta Smaller Than Pulmonary Trunk	Other Cardiac Defects	Edema	Cyanosis	Dyspnea	Recognized Pulmonary Congestion
Vieussens, 1715	36 hr.	Complete	+	+	+	None	–	+	+	+
Smith, 1846	21 hr.	Complete	++ (Ventricle)	+	+	Mitral stenosis	–	+	+	–
Vernon, 1856	4½ hr.	Complete	+	+	–	Interventricular septal defect; overriding aorta; no ductus	–	+	No data	No data
McIntosh, 1926	5 wk.	Complete	+ (Atrium)	+ (Atrium)	++	Mitral atresia, only one ventricle, abnormal vein from left atrium	+	+	+	+
Lehman, 1927	22 hr.	Complete	+	+	+	Aortic valve defective	–	+	No data	–
Bellet and Gouley, 1932	12 hr.	Complete	++	+	++	Aortic atresia, mitral valve defective	No data	No data	No data	No data
Read and Krumbhaar, 1932	Stillborn	Complete	No data	+	+	None	–	..	..	..
Kreutzer and Visillac, 1942	16 hr.	Complete	No data	++	No data	None	–	+	+	+
Hyman, 1946	3½ hr.	Complete	+++	–	++	No left ventricle	–	+	+	+
Edwards and DuShane, 1950	27 days	Complete	++	+	+	Mitral atresia, interventricular defects, abnormal vein from left atrium	–	+	+	+
Authors' Case 1	36 min.	Complete	+++	–	++	Only 2 cusps on aortic valve	–	+	No data	–
Tait, 1876	Few min.	2 mm. slit	No data	No data	No data	None	+	+	Never breathed	–
Osler, 1880	Stillborn	Admits 5 mm. probe	No data	+	+	None	+	..	..	..
Patten, 1938	1 mo.	Small slit	+	No data	+	None	No data	No data	No data	No data
Benner (1), 1939	Stillborn	Admits 3 mm. probe	–	+	No data	None	+	..	..	..
Benner (2), 1939	11 hr.	Admits 4.5 mm. probe	–	+	No data	None	+	+	+	+
Authors' Case 2	4 hr.	2 mm. slit	–	++	+	None	–	+	+	+

congestive failure are those originally labeled as iodiopathic hypertrophy but now recognized as due chiefly to endocardial sclerosis or anomalies of the coronary arteries. As yet no distinctive tests or signs permit an accurate diagnosis of such disorders.

The possibilities of surgical repair of interatrial atresia are likewise not very promising. Even if the patients lived long enough for a diagnosis to be made, it still seems unlikely that a technique could be devised whereby the hypoplastic left atrium and ventricle could be made to assume a normal load of work, or that the "piling-up" of blood in those chambers could be relieved without further burdening the already overtaxed right-sided chambers.

The degree of hypoplasia of the left-sided chambers has been observed to vary considerably (Table) from minute intramural slits as seen in our Case 1 to chambers of normal size such as occurred in our Case 2. This difference may be related to the time in embryonic or fetal life at which the interatrial opening closed. With early closure greater degrees of hypoplasia would be expected. Closure occurring later in fetal life would allow for greater previous cardiac growth and would also more likely be associated with sufficient pulmonary circulation to keep the left side of the heart at least partially filled with blood. In the latter instance the left atrium and ventricle would be more nearly normal in size.

Premature closure of the interatrial foramen may result from any one of three different developmental errors. The first would occur about the 40th day of intrauterine life, when normally the interatrial septum primum should become perforated to form the foramen secundum, shortly before the foramen primum is obliterated by continued caudalward growth of the septum. Failure of the secondary perforation to appear, together with the usual obliteration of the primary foramen would remove all interatrial communication at a very early age. A second possibility for abnormal closure involves the interatrial septum secundum which develops to the right of the primary septum during the third intrauterine month. The secondary septum grows beside and in a plane parallel with the primary septum; but the latter is sufficiently lax that, although the free margin of the septum secundum may completely overlap the foramen secundum, the foramen is not occluded under normal circumstances. In fact, this secondary septum normally ceases growing at about the time it overlaps the secondary foramen. If it does continue growth to form of itself a complete interatrial partition before birth, the result is congenital absence of the foramen ovale, which is characterized not only by absence of an interatrial foramen, but also by the lack of a fossa ovalis and its surrounding limbus. The usual boundaries of the foramen ovale and of the fossa ovalis are marked by the free margin of the secondary septum. In at least four of the cases summarized in the table the patients are known to have had no sign of either foramen or fossa ovalis, and it may be presumed that in these instances the primary fault was overgrowth of the septum secundum. Proper formation of both primary and secondary septa, however, does not assure preservation and proper functioning of the foramen ovale until birth. These two components of the definitive septum, situated side by side and overlapping one another as they do, may become prematurely fused, thus reducing or obliterating the foramen ovale before birth in much the same way as occurs normally after birth.

The cause of prenatal closure of the interatrial foramen, like that of most congenital heart diseases, is unknown. It is of incidental interest to note that a similar

condition has been produced experimentally in rats. The normal perforation (foramen secundum) failed to appear in the interatrial septum primum of several rat fetuses that were subjected to roentgen irradiation in early stages of gestation (Wilson, Jordan and Brent [7]). Had these animals survived until term, it is likely that their hearts would have shown the same hypoplasia of the left chambers and hypertrophy of the right chambers that developed in the human hearts that were likewise deprived of interatrial communication during the prenatal period.

SUMMARY

Prenatal closure of the interatrial foramen causes developmental distortions of the heart which are not compatible with postnatal life for more than a few hours or days. The absence of such a foramen during fetal life deprives the left atrium and left ventricle of all but the relatively small amount of blood brought by the pulmonary veins. This is an insufficient amount to bring about normal dilatation and muscular development of the left-sided chambers, which therefore remain more or less hypoplastic. Such hypoplasia may be tolerated during fetal life, but the increased amounts of blood which shortly after birth begin to flow through the lungs and into the left atrium and ventricle cannot be accommodated by these underdeveloped chambers. Pulmonary venous congestion, accompanied by cyanosis and dyspnea, is the result.

Two cases of prenatal closure of the interatrial foramen have been described. These together with 15 cases found in the medical literature have been compared in regard to clinical manifestations of the patients and the anatomical features of their hearts. The possible manner in which the condition originated in embryonic life has been discussed briefly.

ADDENDUM

Since this paper was submitted for publication two additional cases have been reported by H. Brody (Antenatal Occlusion of Foramen Ovale: Report of 2 Cases, *Am. J. Clin. Path.* **23: 37**, 1953). This author cites another case reported by C. Raeburn (Cardiac Abnormality in the Fœtus, Apparently Resulting from Premature Closing of the Foramen Ovale Due to Pressure of Diaphragmatic Hernia, J. Path. & Bact. **63:** 160, 1951). Thus these three additions bring the total of known cases to 20.

7. Wilson, J. G.; Jordan, H. C., and Brent, R. L.: Effects of Irradiation on Embryonic Development: II. X-Rays on the Ninth Day of Gestation in the Rat, Am. J. Anat. **92**:153, 1953.

TREATMENT OF BACTERIAL MENINGITIS OF UNUSUAL ETIOLOGY AND PURULENT MENINGITIS OF UNKNOWN ORIGIN

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BECAUSE of the rapid development of new clinically-useful antibacterial agents, we have undertaken a series of controlled studies on patients with bacterial infections of the meninges in order to determine which drug or combination of drugs will give optimal results with minimal toxicity, annoyances, and difficulty in the treatment of meningitis caused by various agents. Results in patients treated for Pneumococcus,[1] Bacillus influenzae,[2] and Meningococcus [3] meningitis have been reported previously.

However, the cataloguing of treatment of these three conditions leaves an incomplete picture unless one considers several other pertinent problems.

First, there is a significant group of patients in whom the etiologic agent is other than one of the above-named organisms, and the incidence and response to treatment of these "unusual" infections must be weighed in the over-all planning.

Second, the choice of an agent in patients in whom the diagnosis is established by immediate bacteriologic examination of the spinal fluid is easily made based upon results previously obtained and reported. On the other hand, in a rather large number of patients an exact etiologic diagnosis cannot be achieved before antibacterial treatment is started. In this situation, a choice of drug is made that is most apt to be effective against the probable organisms and, at the same time, will be reasonably safe should a less common bacterium be involved. Changes are made if further bacteriologic studies indicate them.

From the Department of Medicine, University of Illinois College of Medicine, and the Municipal Contagious Disease Hospital.

1. Lepper, M. H., and Dowling, H. F.: Treatment of Pneumococcic Meningitis with Penicillin Compared with Penicillin Plus Aureomycin: Studies Including Observations on an Apparent Antagonism Between Penicillin and Aureomycin, A. M. A. Arch. Int. Med. **88**:489 (Oct.) 1951.

2. Lepper, M. H.; Wehrle, P. F., and Blatt, N.: Treatment of Hemophilus Influenzae Meningitis: Comparison of Aureomycin Alone Versus Aureomycin, Streptomycin and Gantrisin, A. M. A. Am. J. Dis. Child. **83**:763 (June) 1952.

3. Lepper, M. H.; Dowling, H. F.; Wehrle, P. F.; Blatt, N. H.; Spies, H. W., and Brown, M.: Meningococcic Meningitis: Treatment with Large Doses of Penicillin Compared to Treatment with Gantrisin, J. Lab. & Clin. Med. **40**:891 (Dec.) 1952.

Therefore, the incidence and response to treatment of types of purulent bacterial meningitis other than those proved to be caused by pneumococci, meningococci, and influenza bacilli are important. Similarly, the frequency of patients in whom treatment is started before specific etiologic diagnosis is possible should be known.

In this paper figures pertinent to both of these problems are presented and interpreted as to their bearing on the treatment of meningitis.

MATERIAL

All patients reported were treated over a two-year period in the wards of the Municipal Contagious Disease Hospital. Two groups of patients were available for study. First, those with culturally proved etiologic agents other than meningococci, pneumococci, or Hemophilus influenzae. In this group there were 21 patients. When the organism was seen on a stained smear of the spinal fluid sediment, the choice of antibiotic to be used was made on the basis of the tentative diagnosis, and a change in treatment was made only if the clinical course demanded it. On the other hand, if no organisms were seen on smear, the patients were treated according to the likelihood of Hemophilus influenzae being present. Thus, patients with a rash suggestive of meningococcemia and patients over the age of 10 years if only moderately ill were treated with penicillin alone. Patients who were critically ill without rash and over 10 years of age were treated with penicillin and streptomycin. Patients under 10 years of age without rash were treated with aureomycin hydrochloride or penicillin and aureomycin until the latter combination was proved to be detrimental to patients suffering from Pneumococcus meningitis.[1] The regimen used was changed when the results of culture of the spinal fluid or the clinical condition demanded it.

The second group consists of 20 patients in whom the etiologic agent could not be found by either smear or culture of the spinal fluid. These were treated according to the criteria set forth above for those patients whose initial spinal fluid smear was negative for pathogens.

A third group of 17 patients with no demonstrable etiologic agent and much therapy before admission to the hospital are not included, since these patients were well on the way to recovery at the time of admission, and treatment could not be evaluated.

When penicillin is recorded as having been used, the dose was 1,000,000 units of a soluble salt every 2 hours administered intramuscularly or intravenously for several days. When the patient was definitely improving, 600,000 units of penicillin procaine in aqueous suspension was substituted for every third dose for 24 hours, and then the penicillin procaine was continued and the soluble penicillin stopped.

Streptomycin has been given by the intramuscular route at six-hour intervals in the amount of 50 mg. per kilogram per 24 hours in children and 4 gm. a day for 5 days in adults. If the drug was used longer than this, the dose was halved. It was almost always discontinued by the 10th day.

Aureomycin and chloramphenicol have always been given by the intravenous route until definite improvement has occurred. The intravenous dose has been a maximum of 50 mg. per kilogram per 24 hours in divided doses at 6-hour intervals, but not exceeding 2 gm. per 24 hours in adults.

The only drugs given intrathecally have been polymyxin and bacitracin. These drugs have been used intramuscularly, in addition, but their doses have been limited to 2.5 mg. per kilogram per 24 hours and 200,000 units per 24 hours, respectively.

RESULTS

Table 1 gives the incidence of various etiologic agents found among all of the purulent meningitis patients treated over a two-year period. All of the Meningococcus and Hemophilus influenzae patients and 14 of the Pneumococcus patients have been previously reported.[4] Also shown in this table is the frequency of cases in

4. Footnotes 1, 2, and 3.

which an immediate bacteriologic diagnosis could not be made by examination of smears from the spinal fluid and petechiae, if present.

Table 2 records the results in 21 patients treated for specific bacterial meningitis. In the group there were four deaths.

Six of these patients were suffering from beta hemolytic Streptococcus infections, all originating from streptococcal ear infections. As can be seen, results of treatment with penicillin were excellent, even including one patient who was the sickest among the patients who eventually recovered. Because of the small number of patients, no significance is attached to the less favorable response to penicillin plus aureomycin, but certainly the combination has no merit. The patient who died, however, had a fulminating course and had a large abscess in the temporal lobe. It is doubtful if he would have responded to any therapy, since he died 18 hours after the start of treatment.

As would be expected with low-grade pathogens, the alpha hemolytic Streptococcus infections were easily treated. Here penicillin and aureomycin were used in the infant because of the age factor and in the adult because one dose of each drug was given before admission.

TABLE 1.—*Relative Frequency of Purulent Meningitis Caused by Various Agents and the Ability to Make a Positive Etiologic Diagnosis on Admission*

Etiologic Agent	Number of Patients	Per Cent of Total	Patients Without Positive Bacteriologic Diagnosis by Smear Technique	
			Number	Per Cent
Meningococcus	130	52	11	8.5
Pneumococcus	24	10	3	12.5
Hemophilus influenzae	34	14	5	14.7
Other bacteria, excluding tuberculosis	21	9	14	66.7
Not demonstrated	37	15	37	100
Total	246	100	70	28.4

Staphylococcic meningitis was particularly troublesome. One patient, admitted moribund with an illness of only a few hours' duration, died less than 24 hours after onset of illness in spite of treatment with penicillin. Bronchopneumonia was found at autopsy and was presumed to be the portal of entry of his infection. A second patient, who initially responded well to penicillin, had spinal fluid evidence of prolonged infection. Aureomycin was used in the eighth week of illness, four weeks after penicillin had been stopped, to see if recovery could be speeded. There was no abrupt change in the gradual improvement which was occurring. In the third patient with Staphylococcus meningitis it developed in the course of a recalcitrant endocarditis. Bacitracin administered intramuscularly and intrathecally at the time of the meningitis cleared the meninges, but the blood culture remained positive. About six weeks later, after much other therapy, autopsy revealed that the meninges had remained free of infection following the bacitracin treatment.

In each patient with Friedländer's meningitis, chloramphenicol seemed to give the best results of any agent tried and to be responsible for the cure.

The patient with Listeria infection had a diffuse encephalitis in the brain stem and little meningitis. He was moribund on admission, and since signs and symp-

TABLE 2.—*Meningitis Caused*

Etiology by Culture	No. of Patients	No. with Positive Spinal-Fluid Smear	Age Group, Yr.			Initial Treatment		Changes in Treatment
			Under 1	1-40	Over 40	Drug †	No. of Patients	
Beta hemolytic Streptococcus	6	3	0	6	0	P	3	None
						P and A	3	None
Alpha hemolytic Streptococcus	2	0	1	0	1	P and A	2	None
Coagulase-positive Staphylococcus aureus	3	2	0	2	1	P	2	None
						.....	..	1 patient changed to A
						B	1	None
Klebsiella pneumoniae	2	0	0	0	2	P and A	1	A only 2d day; to C 9th day
						P	1	A on 2d day; to O on 4th day; to C on 12th day
Listeria	1	0	0	0	1	S	1	None
Escherichia coli	3	2	2	1	0	A	1	None
						C	2	Px used in 1 patient
Escherichia coli and Pneumococcus	1	Pneumococcus only	0	1	0	P	1	Added S
Alcaligenes	1	0	0	1	0	P and A	1	None
Pseudomonas	1	0	0	1	0	A	1	Added S and Su
Corynebacterium	1	0	0	0	1	P, Su, and A	1	None
Total	21	7	3	12	6			

* Mental states in infants under one year not evaluated.
† P indicates penicillin; A, aureomycin; B, bacitracin; S, streptomycin; C, chloramphenicol; O, oxytetracycline ("terramycin");

toms were suggestive of tuberculous meningitis he was treated with streptomycin, but he died within eight hours.

Among the three patients with Escherichia coli infection, the infection of one was superimposed on a tuberculous meningitis for which the patient was receiving intrathecally administered streptomycin. Treatment with aureomycin was successful enough so that no trace could be found of any infection except the tuberculosis at autopsy, four weeks later. Two infants were treated with chloramphenicol, one of

by Specific Etiologic Agent

Portal of Entry of Infection (No. Patients)	Outcome		Temperature Normal in Hr.			Mental Abnormality *				Spinal Fluid Normal in Wk.				Comment
	Lived	Died	0-72	72-168	Over 168	None Present	Clear in Hr. 0-24	25-48	Over 48	2	3	4	Over 4	
Otogenic (6)	3	0	3	0	0	1	1	0	1	2	0	0	1	One patient had mastoiditis, convulsion, and transient hemiplegia; one had coma, athetosis, and bilateral paralysis and was in shock and moribund 2 days; one died after 18 hours with temporal lobe abscess—meningitis
.....	2	1	0	2	0	2	0	0	0	0	0	1	1	
Fracture at base of skull (1)	2	0	1	1	0	0	0	1	0	1	0	1	0	.....
Bronchopneumonia (1)	0	1	..	..	..	..	..	..	..	..	..	..	..	.....
.....	1	0	0	1	0	1	0	0	0	0	0	0	1	Changed to A in 6th week in unsuccessful attempt to speed recovery; cerebrospinal fluid not normal until 15th week
Endocarditis (1)	1	0				Unable to evaluate				1	0	0	0	Patient had endocarditis; meningitis developed after course of P, A, and S; B intramuscularly and intrathecally cured meningitis; died later of endocarditis
.....	1	0	0	0	1	0	0	0	1	0	0	0	1	Positive spinal fluid culture and fever until 9th day; rapid response to C
.....	1	0	0	0	1	0	0	0	1	0	0	0	1	Cauda equina abscess; slow response to O; relapsed while still receiving O; good response to C; some return of function, especially after Sk and Sd
.....	0	1	..	..	..	..	..	..	..	..	..	..	..	Encephalitis at autopsy with marked brain-stem involvement
Introduced by spinal tap (1)	1	0				Unable to evaluate								Superinfection during tuberculous meningitis therapy; died of tuberculosis; no evident coliform meningitis at autopsy
.....	2	0	2	0	0	0	0	0	0	0	0	1	1	One patient rapidly well on C; other had had 6 weeks of S, P, and O, before admission; no response to C; excellent response to Px, but hydrocephalus developed
Neurodermal sinus	1	0	1	0	0	0	1	0	0	1	0	0	0	Sinus tract excised successfully
.....	1	0	0	1	0	0	0	1	0	0	0	1	0	.....
Introduced by spinal tap	0	1		Never		0	1	0	0		Never			Admitted with infection secondary to diagnostic spinal tap for congenital aneurysm; died 4th day from subarachnoid hemorrhage
Chronic otitis	1	0	0	1	0	0	0	0	1	0	0	1	0	Sulfonamide reaction
	17	4	7	6	2	4	3	2	4	5	0	5	6	

Px, polymyxin; Su, sulfisoxazole (gantrisin®); Sk, streptokinase and Sd, streptodornase.

whom was treated on the third day of life and made a complete recovery. The other had received penicillin, streptomycin, and orally administered oxytetracycline ("terramycin") for six weeks before admission and was admitted with opisthotonos severe enough to force the head to touch the buttocks. There was much pus in the ventricular system and spinal fluid. Chloramphenicol administered intravenously was without effect for three days. Polymyxin administered intramuscularly, intrathecally, and intraventricularly along with streptokinase and streptodornase admin-

istered intrathecally arrested the infection, although the infant has a severe residual hydrocephalus.

One patient with a mixed Esch. coli and Pneumococcus infection and a neurodermal sinus tract responded well to penicillin and streptomycin.

The Alcaligenes infection responded promptly to the combination of penicillin and aureomycin which was used because the cause was unknown on admission.

The one Pseudomonas infection occurred during an investigative study for a leaking cerebral aneurysm. Before the infection was controlled, the child died of a massive subarachnoid hemorrhage.

The Corynebacterium infection responded rapidly to penicillin, sulfisoxazole (gantrisin®), and aureomycin.

Among 20 patients in whom the cause was never established, it seemed likely from the rash present that three had meningococcal infections; three had pneumonia plus meningitis; two had otitis media; two had old skull fractures, and one had bronchiectasis with a cerebral abscess that had ruptured into the meninges. The portal of entry in the other nine was unknown.

Five patients were infants, 10 children, and 5 adults.

Penicillin was used alone in 11 instances; penicillin and aureomycin and penicillin-streptomycin combinations in 3 instances apiece, and penicillin-aureomycin-streptomycin together, aureomycin only, and chloramphenicol only, in 1 instance each.

Among the 11 who received the penicillin alone there were 2 with presumable meningococcic infections, two with pneumonia, two with otitis, and two with skull fractures. The age distribution was two infants, five children, and four adults. The outcome was good in all except two patients. One was the patient with bronchiectasis and ruptured cerebral abscess who died eight hours after admission. The other patient was a 68-year-old man who was doing well until the eighth hospital day, when he apparently had a cerebrovascular accident. He ultimately recovered but has a residual hemiplegia.

Two of the three patients who received penicillin plus aureomycin did well. The third, an infant in whom the diagnosis was missed for five days before admission, received streptomycin in addition on the third hospital day. The child is mentally retarded and has hemiplegia.

Similarly, among the three patients who received penicillin-streptomycin, two did well and the third, also a neglected infant, has residual mental retardation.

The other patients recovered uneventfully. The one patient treated with chloramphenicol only probably had a meningococcal infection.

COMMENT

With the advent of many efficient antibacterial agents in rapid succession, each of which has at least some effect against several types of bacterial meningitis, it has become important to try to find a simple and satisfactory approach to the problem of treatment of a patient with purulent meningitis. In order to formulate such an opinion, it is necessary to consider not only results in patients with Pneumococcus, Meningococcus, and Hemophilus influenzae meningitis, but also to evaluate what

effect utilization of certain schemes of therapy for these have on the other two groups of patients which occur, namely those with unusual etiologic agents and those in whom the cause is not found.

During the period of this study we have treated 34 patients with Hemophilus influenzae meningitis,[2] 24 with Pneumococcus meningitis, 14 of whom are reported elsewhere,[1] and 130 with Meningococcus infections [4] for a total of 246 patients, including the 41 patients reported here plus the 17 without proved cause, but not suitable for therapeutic evaluation. Therefore, patients with an etiologic agent other than the three common types made up 9% of the patients and those without demonstrable cause, 15%. Moreover, among the 41 patients now being considered, in only 7 was the diagnosis possible by examination of a smear of the initial spinal fluid. In addition, 8.5%, 12.5%, and 14.7% of the Meningococcus, Pneumococcus, and Hemophilus influenzae patients had initial smears negative for pathogens. Therefore, in 70 of the 246 patients it was impossible to make a specific etiologic diagnosis before the start of treatment and in 37 of them a cause was never established. The other 33 patients were distributed among all types of cause.

In the treatment of meningitis of known origin, penicillin is probably the best therapy for Pneumococcus infections [1] and, from the results reported here, satisfactory for most Gram-positive cocci, with the possible exception of Staphylococcus infections in which the changing picture of organism sensitivity makes the choice of a drug most difficult. In influenza bacillus infections it would seem likely that either aureomycin,[5] chloramphenicol [5b] or oxytetracycline is a suitable antibotic. Choice of one of these agents over another must await further trial.

In Meningococcus infections, penicillin in doses used in these cases was as effective as the sulfonamides,[3] and the three new antibiotics, aureomycin, oxytetracycline, and chloramphenicol, seem effective, although not tested as extensively.

For the other Gram-negative rod infections, all of the latter three antibiotics seem to be most apt to succeed, with chloramphenicol perhaps the choice in Friedländer's infection. Polymyxin has a definite role in this group, particularly when the others fail.

In general, the infections with no demonstrable etiology are less severe and respond readily to treatment as indicated in this series.

From the above, the following recommendations can be made: An original smear of the spinal fluid should be used as guide for treatment. If the organism is demonstrable, treatment should be followed as outlined above, and no change is necessary unless culture proves the original diagnosis to be wrong, or the patient is not responding well after 48 to 72 hours of treatment.

If no organism is demonstrated and the spinal fluid findings are those of a purulent meningitis, two criteria should govern choice of drug: (1) age of patient and (2) degree of illness. In the age group under 10 years, the most common organism is Hemophilus influenzae, so that one of the antibiotics generally used in these infections should be elected. However, if the child is critically ill and there is good

5. (*a*) Footnote 1. (*b*) Schoenbach, E. B.; Spencer, H. C., and Monnier, J.: Treatment of Hemophilus Influenzae Meningitis with Aureomycin and Chloramphenicol: Experience in 30 Consecutive Cases, Am. J. Med. **12**:263 (March) 1952.

reason to suspect a Pneumococcus infection, such as a concomitant pneumonia with empyema, penicillin should be used and streptomycin may be added to attempt to control the influenza bacillus, should it be the causative agent.

In the age group over 10 and particularly the older ages, the Pneumococcus is by far the most serious offender. If the patient is only moderately ill, penicillin alone seems sufficient but if he is critically ill, streptomycin can be added in case a Gram-negative rod is involved.

Since Meningococcus infections respond well to so many agents, the possibility of their being the cause is no serious consideration in choosing the drug to be used.

If culture establishes the diagnosis, changes in treatment can be guided by the condition of the patient and the etiology. If no organism is established, the course of the patient determines empirical changes in treatment, but these are usually not needed.

SUMMARY

Twenty-one patients with meningitis due to specific etiologies as follows are reported: six due to beta hemolytic Streptococcus, two, alpha hemolytic Streptococcus; three, Staphylococcus; three, Escherichia coli; two, Klebsiella pneumoniae, and one each, Alcaligenes, Corynebacterium, Pseudomonas, Listeria and a mixture of Pneumococcus and Esch. coli. Four of these patients died before the meningitis was cured, all except one within 24 hours. The other patient died of a ruptured cerebral aneurysm.

Twenty other patients with purulent meningitis of undetermined origin are reported, among whom one died of a ruptured cerebral abscess shortly after admission.

Penicillin was satisfactory therapy for most of the coccal infections and most of those of unknown origin. Aureomycin, oxytetracycline ("terramycin"), and chloramphenicol are recommended in the Gram-negative rod infections, with polymyxin an alternative for certain resistant organisms. Staphylococcus presents a problem because of the increasing frequency with which resistant strains are encountered.

Recommendations for managing patients with and without immediate positive bacteriologic diagnosis are made.

Case Reports

USE OF ASPIRATION LUNG PUNCTURE IN DIAGNOSIS OF IDIOPATHIC PULMONARY HEMOSIDEROSIS

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IDIOPATHIC pulmonary hemosiderosis is a rare disease affecting children between the ages of a few months and 16 years; only one case has been reported of this disease occurring in an adult.[1] In an excellent review of the literature, Wyllie, Sheldon, Bodian and Barlow[2] collected 17 previously-reported cases and added an additional 7 cases from the Hospital for Sick Children, London. It is interesting to note that only 4 cases have been reported from the North American continent.[3]

The clinical picture consists of recurrent attacks of fatigue, cyanosis, fever, pallor, and increasing dyspnea which usually occur suddenly and are associated with a marked degree of iron-deficiency anemia with some features suggesting hemolysis; true intravascular hemolysis does not, however, occur.[2] Coughing and vomiting are often prominent symptoms in the acute attacks, hemoptysis and hematemesis have been reported in many cases, and tests for occult blood in the stools may become positive. Transient enlargement of the spleen and liver occurs in some cases, and slight jaundice may follow the acute attacks. The attacks last for a few days, but may pass into a subacute stage which can persist for longer periods. In severe attacks right-sided heart failure may supervene, from which the patient may recover, or which may eventually cause death. In long-standing cases of this disease, evidence of right ventricular hypertrophy is usually present, and clubbing of the fingers may occur.

The changes in the lungs seen on roentgenogram may be quite characteristic, the commonest feature consisting of mottled shadows in the hilar regions and diffuse speckling throughout the peripheral lung fields.[4]

Postmortem examination of the lungs reveals extensive hemorrhages throughout, with generalized invasion of the alveoli by macrophages containing hemosiderin; there is no evidence of hemosiderosis elsewhere in the body. Other notable features are diffuse pulmonary fibrosis and degeneration of the elastic tissue in the alveolar

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3. Anspach, W. E.; Am. J. Roentgenol. **41**:592, 1939. Pilcher, J. D., and Eitzen, O.: Am. J. Dis. Child. **67**:387, 1944. McLelchie, N. G. B., and Colpitts, G.: Canad. M. A. J. **61**:129, 1949. Luther, G.: Cincinnati J. Med. **30**:546, 1949.
4. Footnote 2. Waldenström, J.: Acta radiol. **25**:149, 1944.

walls and in the blood vessels of the lung. These changes in the elastic tissue of the lung have been suggested to be the primary causes of the disease.[2]

Although it is stated that the clinical and roentgenographic picture is quite characteristic,[2] it is interesting to note that in only 11 out of the 29 cases reported was the diagnosis suggested during life, and in only 4 of these were hemosiderin-containing macrophages obtained from the lungs to confirm the clinical impression. In view of this, it was thought that the following case would be of interest, as it emphasizes the importance of diagnostic lung aspiration in suspected cases.

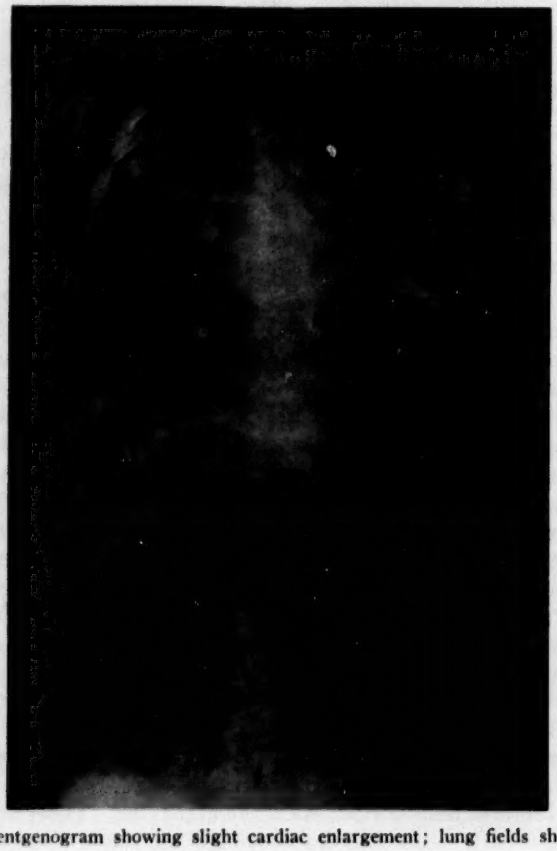

Fig. 1.—Roentgenogram showing slight cardiac enlargement; lung fields show fine diffuse haziness.

REPORT OF CASE

P.MCG., a 2½-year-old Negro boy, was admitted for study of anemia. There was no contributory family history. Prenatal, birth, and neonatal courses were uneventful. Eight months previously, because of bronchitis, a roentgenogram of the chest was taken at another hospital. This revealed bilateral peribronchial infiltration; the hemoglobin and red blood count were reported to be normal. He appeared well for 6 months, then frequent moaning, poor appetite, and failure to play as usual were noted. One month earlier, he was hospitalized because of anemia. Studies were considered compatible with a nutritional anemia, and following transfusions totaling 500 cc. of whole blood, oral administration of iron was started, and the patient was

discharged. One week before admission to this hospital he was noted to be quite pale. There was no known ingestion of drugs and no contact with poisons, nor was there any history of melena, hematuria, hemoptysis, or hematemesis. There was no history of recent infection. He was a well-developed and well-nourished Negro boy appearing restless, but in no distress. His temperature was 100.6 F., pulse rate 140, and respirations 20. Pallor of the skin, mucous membranes, and nail beds was marked. No icterus was present. Slight submaxillary and posterior cervical adenopathy was noted. The heart was slightly enlarged to the left with a grade 1 precordial systolic blow. The spleen and liver were at the costal margin.

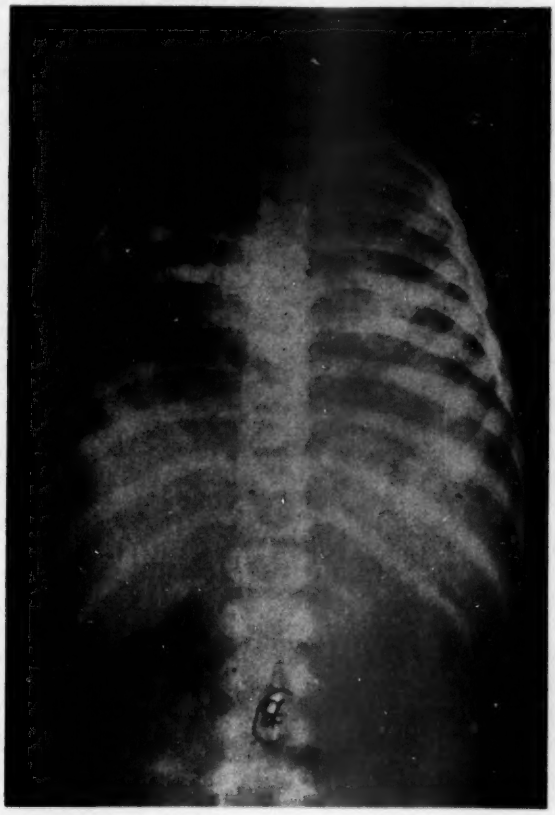

Fig. 2.—Roentgenogram taken two weeks subsequent to Figure 1, showing little change.

Initial laboratory studies were as follows: hemoglobin 3.5 gm. per 100 cc.; red blood count 1,650,000; hematocrit reading of 19%; white blood count 25,700, with normal differential count; reticulocytes 7.5%. Urinalysis, guaiac test of stools, Coombs test, sickle cell preparations, liver function studies, blood cultures, serologic tests for syphilis, tuberculin tests, and roentgenograms of the skull and long bones showed no significant abnormalities. The roentgenogram of the chest confirmed the clinical impression of slight cardiac enlargement; the lung fields showed a fine diffuse haziness (Fig. 1). Red blood cell indices were mean corpuscular volume 97, mean corpuscular hemoglobin 24, and mean corpuscular hemoglobin concentration 25. After two transfusions totaling 200 cc. the hemoglobin was only 4.4 gm. per 100 cc. The pulse ranged from 120 to 140 and respirations from 26 to 60. After further transfusions with packed red cells, the hemogram became normal, yet the rapid pulse and respirations continued. Iron therapy

was started, and the patient was observed for a period of six days, during which time his temperature, pulse, and respirations returned to normal, and he seemed to be having a good response to iron, as evidenced by a reticulocytosis of 9.5%. The interstitial pulmonary infiltration showed no improvement during this time, and the patient was discharged.

He was readmitted two weeks later for further study, having received no therapy at home. Physical findings were essentially unchanged. The hemoglobin was 8.4 gm. per 100 cc., red blood count 3,150,000, white blood count 7,400 with 8% eosinophiles, and reticulocytes 2.4%. The bone marrow showed marked variation in size of red cells, with a few target cells and rare spherocytes. The guaiac test of stools was negative. Incubated and nonincubated osmotic and mechanical fragility studies appeared to rule out acquired and congenital hemolytic disease and produced curves consistent with an iron-deficiency anemia. At this time his serum iron was 65 γ per 100 cc. with a latent iron-binding capacity of 355 γ per 100 cc., a characteristic pattern for an iron-deficiency state.[5] Roentgenograms of the chest showed essentially the same changes noted previously (Fig. 2); fluoroscopy contributed nothing additional to the findings. Electrocardiographic findings were within normal range. Trichina skin tests, stool examinations, and duodenal aspiration for parasites gave negative results. Gastrointestinal and barium enema studies showed nothing significant.

Ten days after admission, his temperature rose to 100.4 F., pulse rate to 150, and respirations to 60. Increasing pallor was noted. The hemoglobin was 2.8 gm. per 100 cc. lower than on admission. Diminished breath sounds were found at the base of the right lung and the scleras were faintly icteric. At this time the diagnosis of idiopathic pulmonary hemosiderosis was suggested by the department of radiology and by several clinicians and since sputum could not be obtained, gastric aspiration was performed. A smear of the contents revealed macrophages containing granules which appeared to be hemosiderin when stained with Wright's stain, but which did not take an iron stain. A lung-puncture aspiration was then performed in the following manner: The skin in the right axilla was cleansed with pHisoderm® (detergent containing hexachlorophene) and prepared with iodine and alcohol. The skin was infiltrated with 2% procaine hydrochloride, and a 20-gauge needle attached to a 10-cc. syringe was introduced into the third interspace. With steady suction, about 0.25 cc. of pink-tinged fluid was obtained and diluted to a volume of 5 cc. with sterile saline. A portion of this was cultured and proved negative; the remainder was smeared and stained with Prussian blue. Macrophages laden with hemosiderin were easily demonstrated (Fig. 3). The patient suffered no ill effects from the procedure and was immediately up and about.

COMMENT

This case presented a clinical and roentgenographic picture suggestive of idiopathic pulmonary hemosiderosis, and the hematological investigations conformed with the findings previously described by other authors. The clinical diagnosis was not confirmed, however, until lung puncture revealed the presence of numerous hemosiderin-containing macrophages in the small amount of lung fluid that was obtained.

Of the 11 cases previously diagnosed during life,[6] typical hemosiderin-containing macrophages were recovered from the lungs in only 4. Hanssen [6c] first discovered such cells in sections prepared from blood-stained sputum, and Wyllie, Sheldon, Bodian, and Barlow [2] found extracellular and scanty intracellular hemosiderin granules in the vomitus of one of their patients. In another, typical cells were discovered when aspiration lung puncture was carried out to exclude tuberculosis. King [6d] has also reported one case in which the diagnosis was confirmed by finding typical cells in the sputum, in gastric washings, and on lung puncture.

5. Serum-iron studies were performed through the courtesy of Dr. Irving Schulman, New York Hospital.

6. (*a*) Footnote 4. (*b*) Nitschke, A.: Klin. Wchnschr. **23**:348, 1944. (*c*) Hanssen, P.: Acta. pædiat. **34**:103, 1947. (*d*) King, A. B.: Proc. Roy. Soc. Med. **42**:87, 1949.

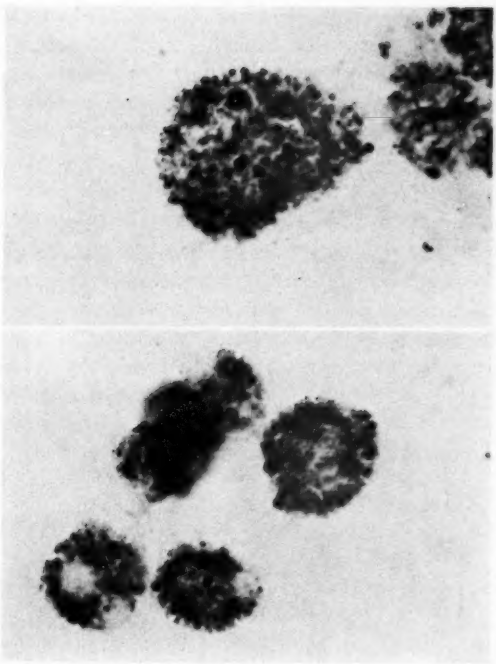

Fig. 3.—Smear obtained by lung puncture aspiration, showing macrophages laden with hemosiderin.

It is apparent that the diagnosis of idiopathic pulmonary hemosiderosis can be confirmed during life by these means. It may be difficult or impossible to obtain sputum from such children; in our case, examination of gastric washings gave equivocal results. Aspiration lung puncture is a simple procedure in these cases and appears likely to give confirmation of the diagnosis. Although there were no untoward sequelae in the two recorded cases in which the patients had lung punctures and in our case, it may be argued that this procedure may not be altogether without danger, especially in view of the suggested origin of the condition. Therefore this should be borne in mind when considering diagnostic measures in such cases, and examination of sputum and gastric washings should always be carried out first in the hope that a diagnosis may be established by these means.

It is perhaps noteworthy that of the 29 reported cases, 16 have been recorded by five different groups of workers; this seems to suggest that the disease is not as rare as it would appear, and that in obscure cases of anemia with pulmonary symptoms examination of sputum, gastric washings, and aspiration lung puncture material for hemosiderin-containing macrophages may reveal the diagnosis in an increasing number of cases.

SUMMARY

A patient with idiopathic pulmonary hemosiderosis is presented.

The clinical diagnosis was confirmed in this case by aspiration lung puncture which yielded macrophages loaded with hemosiderin granules.

In patients with obscure iron-deficiency anemias associated with pulmonary findings examination of sputum or gastric washings for macrophages containing hemosiderin should be performed. If such examinations are negative an aspiration lung puncture should be considered.

NEONATAL GRANULOMA VENEREUM

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THE PURPOSE of this paper is to report a case of neonatal granuloma venereum in which the causative organism was identified in auricular and postauricular abscesses. Although the distinctive granulomatous lesion has previously been reported in infants, it is understandably rare.

It is coincidental that the causative organism in a predominantly venereal disease should have been discovered originally in an extragenital lesion. Donovan,[1] whose name is given to the specific organism of the disease, in 1905 described minute sporozoa within macrophages in scrapings from a granulomatous lesion in the mouth of a ward boy in the Madras General Hospital. McLeod,[2] however, had been the first to describe this lesion clinically in a report of three cases of serpiginous ulceration of the scrotum and adjacent structures (1882). Galloway,[3] in 1897, gave the first microscopic description, but misinterpreted the organisms as granules in the large macrophages. Carter,[4] independently and apparently without knowledge of Donovan's earlier report, also described the protozoa, 15 to 20 in number, occurring in large cells in tissues from the lesions known as "ulcerating granuloma of the pudenda." Since these earlier publications, interest in this disease entity has increased. Grindon,[5] in 1913, is credited [6] with having reported the first cases seen in the United States, even though he stated that R. W. Taylor had already seen the disease in New York. Symmers and Frost [7] recognized Donovan bodies

Department of Surgery (Dr. Scott and Dr. Harper); Department of Pathology (Dr. Jason), Howard University College of Medicine; Armed Forces Institute of Pathology (Dr. Helwig).

1. Donovan, C.: Medical Cases from Madras General Hospital, Indian M. Gaz. **40**:411-414, 1905.

2. McLeod, K.: Précis of Operations Performed in the Wards of the First Surgeon, Medical College Hospital, During the Year 1881, Indian M. Gaz. **17**:113-123, 1882.

3. Galloway, J.: Ulcerating Granuloma of the Pudenda, Brit. J. Dermat. **9**:133-147, 1897.

4. Carter, R.: Ulcerating Granuloma of the Pudenda: a Protozoal Disease, Lancet **11**:1128-1129, 1910.

5. Grindon, J.: Granuloma Inguinale Tropicum: Report of 3 Cases, J. Cutan. Dis. **31**:236-240, 1913.

6. (*a*) D'Aunoy, R., and von Hamm, E.: Granuloma Inguinale, Am. J. Trop. Med. **17**:747-763, 1937. (*b*) Paggi, L. C., and Hull, E.: Metastatic Granuloma Venereum: Report of a Case, Ann. Int. Med. **20**:686-695, 1944.

7. Symmers, D., and Frost, A. D.: Granuloma Inguinale in the United States, J. A. M. A. **74**:1304-1306, 1920.

in two cases in New York, in 1920, and expressed the opinion that these were the first instances in which the disease was indigenous to this country. The clinical picture of these three early cases conformed to that of granuloma inguinale, though no Donovan (or Carter) organisms could be demonstrated. In each of the cases the original diagnosis was phagedenic syphilitic ulcer, as serologic tests in the three were strongly positive for syphilis.

Since Grindon's publication many cases of granuloma inguinale have been reported in this country. In 1923, Gage [8] reviewed the literature on the subject and added four cases. D'Aunoy and von Hamm [9] (1937) in an excellent survey, were able to collect 257 cases previously reported, and added 294 which had been observed in New Orleans in the preceding four-year period.

More recently attention has been focused on the extragenital sites of granuloma inguinale. Fox [9] (1926), in an analysis of 165 cases, found the lesions in nine to have other than genital sites, including cheek, side of neck, nose, throat, and back of the hand. Greenblatt and associates [10] estimated that 6% of the lesions in granuloma inguinale occurred at extragenital sites. There are many other reports of extragenital lesions.[11] This has prompted the trend toward change of the name to granuloma venereum,[12] a move that is desirable on the grounds of accuracy.

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8. Gage, I. M.: Granuloma Inguinale, Arch. Dermat. & Syph. **7**:303-325, 1923.

9. Fox, H.: Granuloma Inguinale: Its Occurrence in the United States, J. A. M. A. **87**:1785-1790, 1926.

10. Greenblatt, R. B.; Torpin, R., and Pund, E. R.: Extragenital Granuloma Inguinale, Arch. Dermat. & Syph. **38**:358-362, 1938.

11. (*a*) Parounagian, M. B., and Goodman, H.: Ulcerating Granuloma (Granuloma Inguinale), Report of a Rare Example of This Disease in a Syphilitic Patient, Arch. Dermat. & Syph. **5**:597-601, 1922. (*b*) Hunter, R. J.: Granuloma Inguinale, with Associated Lesions of the Lip, Pharynx, and Larynx: Report of a Case, Tr. Coll. Physicians (Philadelphia) **45**: 455-465, 1923. (*c*) Lynch, K. M.: Granuloma Inguinale, J. A. M. A. **77**:925-929, 1921. (*d*) Sidlick, D. M.: Granuloma Inguinale of the Face and Mouth, Arch. Dermat. & Syph. **15**:703-708, 1927. (*e*) Sequeira, J. H.: Case of Granulomatous Swellings of the Left Angle of Mouth and in Right Inguinal Region, Proc. Roy. Soc. Med. **1**:92, 1908. (*f*) Lyford, J., III; Scott, R. B., and Johnson, R. W., Jr.: Polyarticular Arthritis and Osteomyelitis Due to Granuloma Inguinale, Am. J. Syph. **28**:588-610, 1944. (*g*) Thierfelder, M. U., and Thierfelder-Thillot, M.: Studien über das venerische Granulom, Arch. Schiffs- u. Tropen-Hyg. **28**:221-235, 1924. (*h*) Thierfelder, M. U.: Beiträge zur Kenntnis des venerischen Granuloms, ibid. **29**:690-698, 1925. (*i*) Packer, H.; Turner, H. B., and Dulaney, A. D.: Granuloma Inguinale of Vagina and Cervix Uteri with Bone Metastases, J. A. M. A. **136**:327-329, 1948. (*j*) Jennison, D. B.; Helwig, E. B., and Milstone, J. H.: Granuloma Inguinale Involving Buttock and Lymph Node: Cultivation of Donovan Body in Embryonic Yolk, Arch. Dermat. & Syph. **55**:342-354, 1947. (*k*) Henthorne, J. C.: Granuloma Venereum, South. M. J. **32**:614-618, 1939.

12. (*a*) Pund, E. R.; Smith, A. D.; Hicks, D. Y., and Dienst, R. B.: Extragenital Granuloma Venereum: Report of Case, South. M. J. **32**:917-919, 1939. (*b*) Pund, E. R., and Greenblatt, R. B.: Granuloma Venereum of Cervix Uteri (Granuloma Inguinale) Simulating Carcinoma, J. A. M. A. **108**:1401-1402, 1937. (*c*) Pund, E. R., and Gotcher, V. A.: Granuloma Venereum (Granuloma Inguinale) of Uterus, Tubes and Ovaries, Surgery **3**:34-40, 1938. (*d*) Arnell, R. E., and Potekin, J. S.: Granuloma Inguinale (Granuloma Venereum) of the Cervix: Analysis of 38 Cases, Am. J. Obst. & Gynec. **39**:626-635, 1940. (*e*) Henthorne.[11k]

Little mention has been made, however, of the possible neonatal manifestation of the disease. Pund and McInnes [13] and Arnell and Potekin [12d] referred to a case reported by Towles: Granuloma venereum was present in the umbilicus of a 6-week-old boy. The case to be presented here is one in which there were multiple lesions involving umbilicus, penis, postauricular region, and radius of a 5-month-old infant.

REPORT OF A CASE [14]

Clinical Data.—An infant boy was admitted to Freedmen's Hospital on Sept. 6, 1946. The supposed mother, the woman who had brought the baby to the hospital, stated that about one month previously he had contracted a cold which was followed by a discharge from the right ear and postauricular swelling. The diagnosis on admission was acute suppurative otitis media. According to the "mother" the birth of the child was normal, both parents were healthy, and the infant had developed normally.

On admission the infant appeared to be well developed and well nourished although fretful. The temperature was 101 F., pulse rate 100, and respiration 28. There was a large tender mass behind the right ear, and exudate came from the right external auditory canal. A perforation was visible in the tympanic membrane.

Fig. 1.—Appearance of large tender postauricular mass with exudate from the external auditory canal before treatment.

On examination of the blood, hemoglobin was 65 mg. per 100 cc., erythrocytes 3,400,000, and leucocytes 10,000, with myelocytes 10%, mononuclear cells 25%, transitional cells 19% and neutrophiles 46%.

The patient was given 40,000 units of penicillin every 3 hours, with no appreciable change in the appearance of the lesions. On Sept. 26, sulfadiazine, 3 grains (0.19 gm.) every four hours, was also given. On Oct. 4, the mass behind the right ear, which had become fluctuant, was incised and drained. A culture of the drainage revealed Staphylococcus aureus and Staph. albus. On Oct. 18, drainage from the left ear was noted, but it abated spontaneously. Granulation tissue, which had filled the site of the abscess by Nov. 1, was removed and examined. Ulcers approximately 1 cm. in diameter were noted on Dec. 7; one at the umbilicus, the other on the dorsum of the penis. These had begun as papules which gradually increased in size before ulcerating. At the same time the right forearm was swollen, and the baby behaved as if in pain. The radial side of the arm was involved in a swelling which appeared to originate in the bone. The overlying skin was warm and glistening, but without evidence of suppuration. The x-ray of the forearm showed destruction of a large part of the shaft of the radius by a

13. Pund, E. R., and McInnes, G. F.: Granuloma Venereum: Cause of Death: Report of 6 Fatal Cases, Clinics **3**:221-234, 1944.

14. Armed Forces Institute of Pathology accession No. 185719.

central lesion with considerable periosteal reaction. It was fusiform in shape, with a tendency to ray formation. Although no definite diagnosis was reached, the differential diagnosis was between Ewing's sarcoma and tuberculosis. Biopsy was not attempted, but 3 erythema doses of x-ray were given for diagnostic as well as beginning therapeutic purposes. Each x-ray treatment was followed by increase in the size of the radial lesion. During this time the infant continued to have intermittent fever. From admission to the end of January, he was given

Fig. 2.—Same area as Figure 1 after treatment with stibophen (fuadin®) and streptomycin. Stibophen caused partial healing.

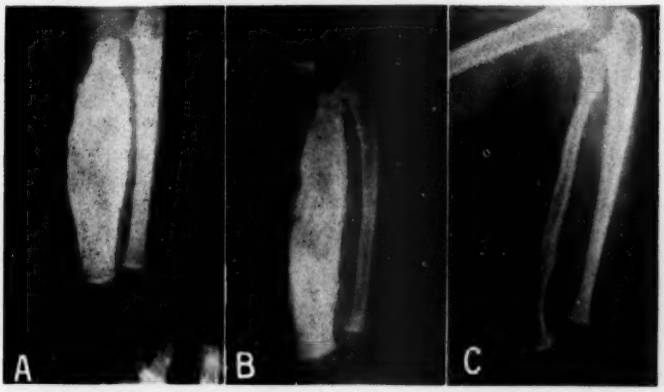

Fig. 3.—*A*, x-ray appearance of lesion of right radius. Initially shaft shows destruction by a central lesion associated with periosteal reaction. *B*, diminution of lesion two months after administration of stibophen. *C*, return of normal configuration of radius eight months after administration of stibophen.

courses of penicillin totalling 9,000,000 units, but the postauricular lesion remained an angry granulating ulcer, and the penile and umbilical lesions were unchanged.

On Jan. 23, 1947 the hemogram showed erythrocytes 4,500,000, hemoglobin 10.5 gm. per 100 cc., 31,850 leucocytes, including large lymphocytes 3%, eosinophiles 0.5%, basophiles 0.5%, polymorphonuclear neutrophiles 35%, stab cells 16%, small lymphocytes 31%, and myelocytes 0.15%. Platelet count was adequate. Anisocytosis and poikilocytosis were noted. Plasma

proteins were 7.78 gm. per 100 cc., inorganic phosphorous 3.7 mg., and calcium 9 mg.; alkaline phosphatase was 6.8 units. The Kahn and tuberculin tests were repeatedly negative.

After the three x-ray treatments had failed to produce any resolution of the process in the right arm, and because the microscopic picture suggested lymphogranuloma venereum, stibophen (fuadin®) therapy was begun on Feb. 7, 1947, in 2 cc. doses daily for two-week periods. Four such courses were given at intervals of a week. Following the second course of stibophen, the lesion of the right radius began to shrink. The postauricular, umbilical, and penile lesions definitely regressed, although they did not heal completely. An x-ray of the radius on June 30, 1947, showed shrinkage of the mass and the return of the bone to its normal configuration.

Pathologic Features.—The material from behind the right ear, consisting of numerous fragments of soft red tissue, was examined pathologically. The tissue was fixed in a solution of 10% formaldehyde. Paraffin sections were prepared and stained with hematoxylin and eosin, with the Giemsa stain, and by the Warthin-Starry method.

Microscopic examination of the preparations stained with hematoxylin and eosin showed a uniform picture of richly vascularized granulation tissue. The stroma between the blood vessels was scanty and infiltrated with inflammatory cells, generally including a large number of mononuclear cells having medium-sized, round, or oval nuclei and a pink, tenuous, often vacuolated, and foamy cytoplasm. Scattered throughout the granulation tissue in varying numbers were polymorphonuclear leucocytes. Frequently these leucocytes were collected in small groups to form so-called microabscesses. Plasma cells and lymphocytes were sparse or absent. Bacillary bodies were occasionally identifiable within the cytoplasm of the mononuclear cells in the hematoxylin and eosin preparation and somewhat more often with the Giemsa stain. These bodies were most readily noted in the Warthin-Starry preparation, where they sometimes filled the cytoplasmic space or were scattered through a vacuolated cytoplasm. Occasionally cells appeared to have ruptured and the bacillary bodies were in the extracellular space.

A few of the fragments of granulation tissue were partially covered with epidermis that exhibited pronounced acanthosis with elongation of the rete pegs. Where the epidermis was ulcerated, the base of the ulcer was comprised of granulation tissue profusely infiltrated with polymorphonuclear leucocytes and mononuclear cells. There were scattered areas of red blood cell extravasation, particularly prominent near the surface of the ulcer. Within an occasional mass of granulation tissue there was a small fragment of partially necrotic bone surrounded by new bone formation.

On the basis of the presence of bacillary bodies within mononuclear cells and the type of tissue reaction, a diagnosis of granuloma venereum was made.

Further Clinical Data.—In October, 1947, it came to our attention that the true mother of the infant had not brought him to the hospital. She was found to be a patient at Gallinger Municipal Hospital, where she was being treated for granuloma venereum. A birth history from Gallinger revealed that April 2, 1946, the mother had been admitted to the "dirty" obstetrical ward because of a granulomatous lesion of the vulva. This had first appeared in February, 1946, and had gradually increased in size. A large lesion was present on each labium minus, and another at the fourchette. Shortly after admission the woman delivered precipitately, before adequate preparation could be made. A third-degree tear occurred at the fourchette, and the infant came in contact with the traumatized infected granulomatous areas. A biopsy of the vulvar lesions revealed Donovan bodies.

In January, 1948, the administration of 10 gm. of streptomycin in 90 mgm. doses every four hours resulted in complete healing of the recalcitrant postauricular, penile, and umbilical lesions of the child. They became epithelized and have remained so. Paralysis of the right side of the face, first noted Feb. 2, 1947, has persisted without improvement.

COMMENT

In the absence of positive demonstration of Donovan bodies from each site, it is impossible to state unequivocally that all of the lesions in this case were due to granuloma venereum. The simultaneousness of their appearance coupled with their uniform response to specific therapy, however, indicates a common etiologic

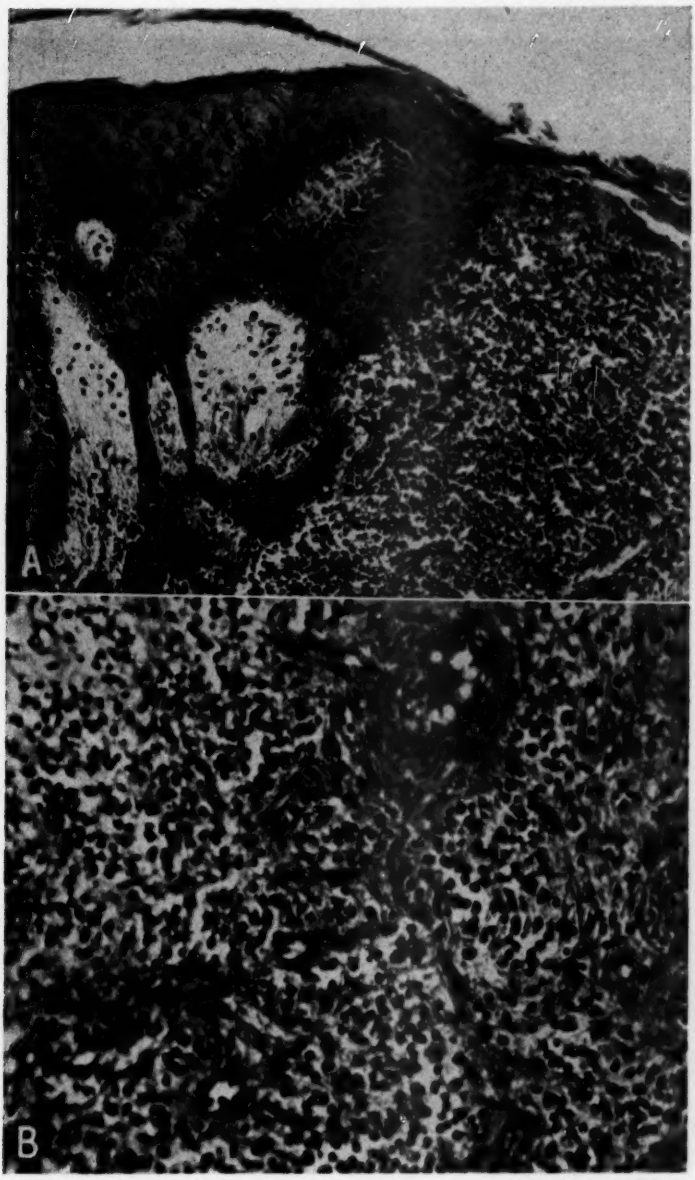

Fig. 4.—Postauricular ulcer. *A*, acanthosis of the marginal epidermis and infiltration of the corium with inflammatory cells. Hematoxylin and eosin; × 125. *B*, vascularized granulation tissue and microabscesses rich in polymorphonuclear leucocytes. Hematoxylin and eosin; × 205.

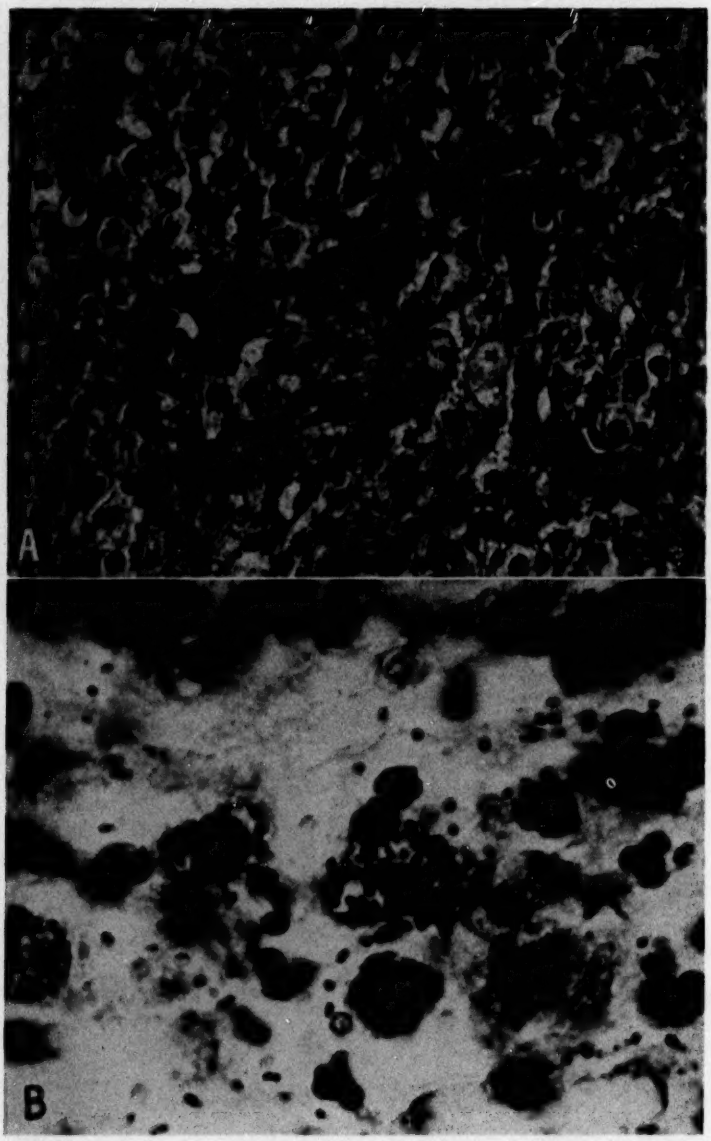

Fig. 5.—Postauricular ulcer. *A*, numerous mononuclear cells within the inflammatory infiltrate. Hematoxylin and eosin; × 515. *B*, mononuclear cells filled with Donovan bodies. Hematoxylin and eosin; × 1500.

background. This implies acceptance, especially for the radial lesion, of the concept that the organism may be disseminated by the blood stream. This has been proved by Packer and associates [11i] in a reported case of widely disseminated lesions involving the knee, hand, elbow, bladder, cervix, and soft tissues of the hand. Lyford and associates [11f] described three cases in which polyarticular arthritis and osteomyelitis were due to granuloma venereum, confirmed by biopsy and tissue culture. They quote Thierfelder and Thillot [11g] and Thierfelder [11h] who reported similar cases in 1924 and 1925, respectively. Paggi and Hull [6b] also described a case with metastatic osseous lesions, in which biopsy from each site was positive. In the case of a 19-year-old woman reported by Packer and associates [11i] abortion was followed by extensive pelvic lesions, perirectal abscess, and lesions in the right knee and knuckle of the left hand, left elbow, bladder, and cervix. Blood cultures employing tryptose-peptone-egg agar showed organisms having the morphologic appearance of Donovan bodies.

Granuloma venereum presents a definite hazard to pregnancy and delivery. Pund and McInnes, 1944,[18] reported a 14.3% mortality. Wilson, 1930, reported five infant deaths in 14 deliveries of mothers with the disease.[15] Among the antibiotics, penicillin has been found to be of little value in the treatment of granuloma venereum by Nelson, 1944,[16] and in our own case. In our patient the lesions definitely regressed on stibophen and healed completely with the addition of streptomycin. More recently it has been reported that chloramphenicol (chloromycetin®) is effective.[17]

SUMMARY

A case of neonatal granuloma venereum involving the right postauricular area, right radius, umbilicus, and penis in a 5-month-old infant is reported. As far as can be determined, this is the first such reported case.

15. Wilson, L. A.: Pregnancy and Labor Complicated by Granuloma Inguinale, J. A. M. A. **95**:1093-1095, 1930.

16. Nelson, R. A.: Penicillin Therapy in Granuloma Inguinale, Am. J. Syph. **28**:611-619, 1944.

17. Greenblatt, R. B.; Wommock, V. S.; Dienst, R. B., and West, R. M.: Chloromycetin in the Therapy of Granuloma Inguinale, Am. J. Obst. & Gynec. **59**:1129-1133, 1950.

Progress in Pediatrics

HYPERVITAMINOSIS A

A Review with a Discussion of Vitamin A

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It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what directions we may look for fruitful investigations in the future.

—WILLIAM OSLER, Gulstonian Lectures, 1885.

I. CLINICAL HYPERVITAMINOSIS A

A. INTRODUCTION

IT HAS long been known among Eskimos and arctic travelers that the ingestion of polar-bear liver may cause illness. One of the earliest descriptions of this disorder was mentioned by the arctic explorer, Elisha Kane,[1] in 1857:

when I was out in the Advance with Captain De Haven, I satisfied myself that it was a vulgar prejudice to regard the liver of bear as poisonous. I ate of it freely myself and succeeded in making it a favorite dish with the mess. But I find to my cost that it may sometimes be more savory than safe. The cub's liver was my supper last night, and today I have the symptoms of poison in full measure—vertigo, diarrhoea and their concomitants.

I may mention, in connection with the fact which I have given from my journal, that I repeated the experiment several times afterwards, and, sometimes, but not always, with the same result. I remember once, near the Great Glacier, all our party sickened after feeding on the liver of a bear that we had killed; and a few weeks afterward, when we were tempted into a similar indulgence, we were forced to undergo the same penance.

It was not until 1951 that the significance of the symptoms of vertigo in Kane's account and of headache in the following passage became in part understandable. In 1899, the explorer, Frederick Jackson,[2] in his book "A Thousand Days in the Arctic," recounts two experiences of the type of illness that befell the members of his expedition.

The doctor and I ate a little fried bear's liver for breakfast; the others did not fancy it. This has been held by many arctic explorers to have poisonous qualities, and he and I desired to test it. We ate about a quarter of a pound each, and although I suffered from a bad attack of headache six hours after, I am not quite sure that the liver produced this unpleasant effect upon me, but intend to further test it.

The doctor has headache also. It may be the liver that is troubling both of us.

From the Childrens Hospital and the Department of Pediatrics, University of Southern California School of Medicine, Los Angeles.

1. Kane, E. K.: Arctic Explorations, Philadelphia, Childs and Peterson, 1857, Vol. 1, p. 392.

2. Jackson, F. G.: A Thousand Days in the Arctic, New York, Harper & Brothers, 1899, Vol. 1, pp. 80, and 105.

Some weeks later, he relates:

Last night at 7 p. m. we had some fried bear's liver again after it had been soaked in boiling water, served with a joint of bear. At 12:30 tonight during my watch a severe headache (both frontal and at the crown of the head) came on with a feeling of nausea. This continued until 3 a. m. when my watch ended and I turned in, and, with the exception of some headache, I had recovered at 9 a. m., when I turned out. I had about three ounces of liver.

Additional descriptions by Jackson of the symptoms of the five men who participated in the same meal were similar to his own. One vomited twice and his illness was slightly prolonged; another ate sparingly and soon recovered.

Lindhard [3] (cited by Rodahl) has reported another expedition in 1913 in which 19 men became ill after eating a stew containing bear liver. The symptoms included drowsiness, sluggishness, irritability, an irresistible desire to sleep, and severe headache and vomiting. On the second day, the skin of 10 men began to peel around the mouth, beginning in spots and gradually spreading over larger areas. In some cases the peeling was confined to the face, but in several it was general. Other explorers have reported one or more of the symptoms mentioned in these three accounts.

In 1942, Rodahl and Moore [4] identified the toxic substance in polar-bear liver. In an expedition to northeast Greenland, specimens of polar-bear liver were collected and on chemical and biological examination were found to be very rich in vitamin A, as also was a specimen of liver from a certain seal (Phoca barbata). The specimens were preserved in brine, small portions were digested with alkali, and vitamin A was extracted. The liver from a 2-year-old female contained 18,000 I. U. units per gram of wet material and a similar result was obtained from a 4-year-old male. A third specimen showed 13,000 units per gram and the same amount was found in seal liver. Carefully planned tests with rats were difficult because of the reluctance of these animals to eat the liver. One rat ate a total of 33.1 gm. during a period of 22 days, amounting to about 15,000 units of vitamin A daily. When moribund it was killed, and at autopsy a profuse internal hemorrhage was found, particularly under the skin but also in the pericardium. Another rat ate 5.3 gm. of liver during a period of nine days and then bled to death after accidentally cutting its paw on the side of the cage. The wound appeared too slight to cause death in a normal animal. A third rat ate 24 gm. of liver in 22 days without any ill effects. It was estimated that if 100,000 units of vitamin A are sufficient to cause immediate illness in rats, then about 7,500,000 units should cause illness in man. This amount would be present in 375 gm. of bear liver containing 20,000 units of vitamin A per gram, not an excessive portion to be eaten at a single meal. In 1947 Rodahl [5] repeated the experiment with two specimens of bear liver from Greenland. One contained 26,700 units and the other 21,900 units of vitamin A per gram of wet material. Ingestion by rats produced the characteristic toxic symptoms in all cases, but when the liver was subsequently freed of its vitamin A

3. Lindhard, J.: Health Conditions on the Denmark Expedition, Medd. om Grønland **41**:461, 1913.

4. Rodahl, K., and Moore, T.: The Vitamin A Content and Toxicity of Bear and Seal Liver, Biochem. J. **37**:166, 1943.

5. Rodahl, K.: Toxicity of Polar Bear Liver, Nature, London **164**:530, 1949; The Toxic Effect of Polar Bear Liver, Norsk Polarinstitutt, Skrifter Nr. 92, 1949.

content, no toxic symptoms resulted. It should be noted that the symptomatology following a single massive dose is quite different from manifestations of subacute or chronic poisoning.

The final link in the food chain that leads to polar-bear-liver poisoning is the source of vitamin A in the diet of this animal. It has been well established that the green plants of the water as well as those of the land synthesize this vitamin under the influence of sunlight. These diatoms, minute algae, and other tiny aquatic plants become food for a group of small sea organisms and the latter in turn for larger species on which the cod and halibut feed. Rachel Carson [6] has described this strange drifting community called plankton, comprised of minute sea organisms and the microscopic plants which sustain them. She tells how the food chain leads on from the plankton to the schools of plankton-feeding fishes like the herring and mackerel; to the fish-eating fishes like the blue fish, tuna, and sharks; to the pelagic squids that prey on fishes, and to the great whales. In the Arctic waters there exist dense plankton swarms with copepods and swimming snails that lure the herring and mackerel, the whale and the seals. In the larger fish, the carotene of the aquatic plants and certain pigments which originate from carotene become converted and stored as vitamin A.[7] And lastly, it is the polar bear that feeds chiefly on the seals, fishes, and other animals.

Among the earliest descriptions of hypervitaminosis A produced experimentally in animals is the report in 1922 by Mouriquand and Michel (cited by Mouriquand).[8] In an attempt to determine in guinea pigs the possible inhibitory action of cod-liver oil on vitamin C, they added an enriched cod-liver oil to a scorbutigenic diet. No cod-liver oil was given to the control group. The animals receiving oil developed symptoms considered characteristic of scurvy well in advance of the controls. In addition to the hemorrhagic lesions, there appeared spontaneous fractures and a generalized fragility of the osseous system. In the years that followed, a great many reports on experimentally-produced hypervitaminosis A were published and have been included in the excellent reviews by Clausen [9] and by Josephs.[10] It became apparent that the lack of uniformity in symptomatology was due to many factors, including age, weight, previous diet of the animals, the ability of the intestine to absorb vitamin A, the medium in which the vitamin A was dispensed, and the amount of the daily and total dose of vitamin A. Moreover, opinions were divided as to whether the toxicity was due to vitamin A or to some accompanying impurity. The clinical picture in animals consists in general of loss of weight, skin lesions ranging from a slight roughening of the hair to alopecia, seborrhea and peeling at the corners of the mouth, dryness and cracking of the mucous membranes, enteritis, emaciation, hemorrhagic manifestations, spontaneous fractures, and generalized bony fragility. The hemorrhages occur as epistaxis, conjunctival, subcutaneous, intramuscular, uterine, and massive internal bleeding. Exophthalmos

6. Carson, R. L.: The Sea Around Us, New York, Oxford University Press, 1951, pp. 19-22.

7. Bessey, O. A., and Wolbach, S. B.: Vitamin A Physiology and Pathology, in The Vitamins, Chicago, American Medical Association, 1939.

8. Mouriquand, G.: Sur L'Hypervitaminose A, Presse méd. **56**:737, 1948.

9. Clausen, S. W.: The Pharmacology and Therapeutics of Vitamin A, in The Vitamins, Chicago, American Medical Association, 1939.

10. Josephs, H. W.: Hypervitaminosis A and Carotenemia, Am. J. Dis. Child. **67**:33, 1944.

was noted by a few observers. It was not until 1943 that Moore and Wang [11] were able to test the toxicity of pure vitamin A in the form of crystalline vitamin A acetate. They administered daily doses of 25,000 to 50,000 units to young rats 69 to 79 gm. in body weight and invariably produced bony fractures after periods of 8 to 20 days. Doses of about 50,000 units given to adult pregnant rats did not cause breakage of bones, but gave rise to fatal uterine hemorrhage.

A few reports appeared of skin lesions following large doses of cod-liver oil in children. One such observation was published by Czerny [12] (cited by Clausen) in 1912. He gave a daily dose of 80 cc. to each of a group of tuberculous children and frequently observed the development of seborrheic dermatitis of the face and scalp. There has been an occasional report of vitamin A poisoning in an adult following the ingestion of a single massive dose. Getz and his associates [13] administered 50 cc. of halibut-liver oil (2,000,000 units of vitamin A) in a single dose to four adults. One individual was considered normal, and the remaining three were diagnosed as having borderline vitamin A deficiencies when tested by biophotometric methods. All experienced dull headaches, but no other symptoms. Rodahl and Moore [4] mention one of the men engaged in the manufacture of halibut-liver oil at the Crookes Laboratories who took without instruction 4 to 5 oz. (115 to 140 gm.) daily. After five days, he became severely ill, the main symptom being giddiness. The daily dose was about 6,000,000 units. After use of the oil had been discontinued, he rapidly recovered and appeared normal after 8 to 10 days.

At the annual meeting of the American Pediatric Society in 1949, the late J. M. Lewis, a distinguished investigator in vitamin research, remarked that in the United States there are probably more individuals with hypervitaminosis A than with vitamin A deficiency. Caffey [14] has recently listed 22 reported cases of hypervitaminosis A and has seen x-rays of many more such patients from all parts of the country. Five unreported cases of chronic vitamin A poisoning have been seen at the Childrens Hospital in Los Angeles. Culver [15] called attention to the magnitude of vitamin consumption in this country. The sale of vitamins during 1947 amounted to $188,000,000, of which $26,000,000 were sold by mail-order houses, department stores, grocery stores, and variety stores. A 300% increase in the sale of costly high-potency preparations occurred between 1945 and 1947. The ease of administration has favored the use of concentrates although there exists an impression, shared by many physicians, that during infancy reactions to plain cod-liver oil, such as vomiting and rashes, are being seen more frequently today than in the past. Greater absorption and storage of vitamin A has been demonstrated when an aqueous dispersion replaces a preparation with an oily base. Belief in the theories that vitamins in addition to those contained in a general diet improve health, increase resistance to infection, and hasten convalescence from any type of illness unfortu-

11. Moore, T., and Wang, Y. L.: The Toxicity of Pure Vitamin A, in Proceedings of the Biochemical Society, Biochem. J. **37**:viii, 1943.

12. Czerny, A.: Beitrag zur Lebertrantherapie, Therap. Gegenw. **80**:49, 1912.

13. Getz, H. R.; Hildebrand, G. B., and Finn, M.: Vitamin A Deficiency in Normal and Tuberculous Persons: As Indicated by the Biophotometer, J. A. M. A. **112**:1308, 1939.

14. Caffey, J.: Vitamin A Poisoning, Editorial, Am. J. Roentgenol. **67**:818, 1952.

15. Culver, P. J.: Vitamin Supplementation in Health and Disease, New England J. Med. **241**:970, 1949.

nately remains firmly fixed in the public mind. Culver has emphasized that vitamin A continues to be prescribed for so-called signs of vitamin A deficiency that are no longer considered valid. These include thickening of the bulbar conjunctivas and a variety of skin lesions, especially keratosis pilaris. The huge stores of vitamin A in the liver of man are maintained not only by the excellence of the American diet and vitamin supplementation, but also by vitamin-enriched foods and by the administration of vitamins to poultry and dairy animals and to nursing mothers. That this has led to a potential state of vitamin A excess in the general population is without positive proof. A psychogenic factor, previously emphasized by Josephs,[10] has been present in some of the cases of hypervitaminosis A. This is manifest as an abnormal craving for certain foods with high contents of carotene. Faulty histories of the precise amount of vitamin intake constitute the commonest cause of diagnostic errors in this disorder. There is evidence that the disease is by no means as rare as the reports in the medical literature would indicate.

The following classification is based on the clinical information now available:

Acute Hypervitaminosis A { Infant / Adult

Chronic Hypervitaminosis A { Infant / Adult

B. Acute Hypervitaminosis A

1. *Infant.*—Acute hypervitaminosis A during infancy occurs in connection with the accidental ingestion of large single doses of vitamin A. It has been noted by Bills (cited by Caffey[14]) that transient nausea and vomiting will occur when children swallow an entire bottle of fish-liver concentrate. In May 1951, Marie and Sée[16] reported three cases of the acute form in infants aged 7½ months, 3½ months, and 3 months, respectively. In addition to the symptoms of vomiting and drowsiness, there occurred a marked bulging of the fontanelle. This was observed by the parents and constituted the basis for seeking medical attention. No cervical rigidity, neurologic signs, or fever developed during the illness. After repeated questioning, it was revealed that within 24 hours prior to the onset of symptoms, each child had received in the feedings the contents of an ampoule containing 350,000 units of vitamin A and 300,000 units of vitamin D. Lumbar puncture showed clear fluid and no abnormal elements. Recovery followed in one or two days. No blood or spinal fluid vitamin A determinations were made. The authors concluded that vitamin A was the causative factor and received partial corroboration from the observation of the following case:

A baby aged 2 months with a mild nasopharyngitis was treated by the instillation of nose drops containing 50,000 units of vitamin A per gram and only a small amount of vitamin D. It was estimated that during a six-day period she received 300,000 units of vitamin A. The fontanelle became full and tense without any associated symptoms. Improvement followed the removal of clear fluid by lumbar puncture. An additional case reported by Dr. M. L. Jammet is included in this article as a footnote. She observed a boy, aged 6 months, who had received in the afternoon one-half ampoule of a preparation amounting to 175,000 units of vitamin A and 150,000 units of vitamin D. During the night the infant cried and behaved in an abnormal fashion. The following morning it was noted that the fontanelle was bulging to a degree that

16. Marie, J., and Sée, G.: Hydrocéphalie aiguë bénigne du nourrisson après ingestion d'une dose massive, unique, de vitamines A et D, Semaine hôp. Paris **27**:1744, 1951.

shocked the mother. No cervical rigidity or Kernig's sign was present. The child was fretful and irritable. Lumbar puncture showed clear fluid and recovery followed in a few days. The mechanism of the increased volume of cerebrospinal fluid remains entirely unknown. The resemblance of these manifestations to the clinical course of polar-bear liver poisoning was emphasized by the authors.

A similar case [17] has been observed at the Childrens Hospital. A Negro boy, aged 7 weeks, was admitted on June 11, 1952, with the complaint of a bulging fontanelle. He was born prematurely and at birth weighed 4 lb. 15 oz. (2240 gm.). No neonatal difficulties were experienced. The feeding consisted of a powdered milk (olac®) containing 0.1% halibut-liver oil. At one month of age, the mother was instructed to give the child 10 drops daily of a vitamin preparation, percomorph liver oil, containing not less than 60,000 units of vitamin A and 8,500 units of vitamin D per gram. She misunderstood her physician's instructions and gave 10 drops five times daily for the three weeks immediately preceding admission. On the day of admission, while bathing the baby, she noticed the markedly bulging fontanelle and brought the child to the hospital. There was no history of fever, lethargy, anorexia, vomiting, diarrhoea, or convulsions.

His temperature was 99.2 F.; pulse rate, 152; respiration, 64; weight, 10 lb. 12 oz. (4880 gm.). The head measured 39.5 cm. and the chest 36.5 cm. He was a healthy-appearing infant. The anterior fontanelle bulged upwards a distance of 2 cm. The liver edge could be felt 3 cm. below the costal margin. Tremors appeared in all extremities whenever the child was disturbed. An easily-obtained sustained bilateral ankle clonus was present. There was no cervical rigidity, and Kernig's sign was negative. Examination otherwise showed no significant abnormalities. The spinal fluid on admission showed a greatly-increased pressure, 30 cells, of which 98% were lymphocytes, a slightly positive Pandy test, and no bacterial growth. Two days later, the spinal fluid still showed increased pressure, 18 cells, with 78% lymphocytes, protein 7 mg. per 100 ml., and sugar 67 mg. per 100 ml. The serum vitamin A level taken the morning after admission was 715 units and four days later, after the discontinuance of vitamin administration, 217 units. On the fifth day after admission the sedimentation rate was 26 (Westergren); alkaline phosphatase, 14.5 Bodansky units; total lipids, 580 mg. per 100 ml.; prothrombin time, 20 seconds; control 15.3 seconds, and a repeat spinal fluid examination showed 3 cells. X-rays showed no bone lesions. The resemblance of the case to that of the patients described by Marie and Sée, the history of excessive vitamin A intake, and the elevated serum vitamin A level led to a final diagnosis of acute infantile hypervitaminosis A. During the week of hospitalization, the irritability diminished and the bulging fontanelle disappeared. A sensation of fulness over the fontanelle persisted. Two days before discharge a fine cutaneous desquamation developed over the trunk and extremities. The comparative measurements of the circumference of the head and chest suggested a mild degree of hydrocephalus.[17a]

2. *Adult.*—Acute hypervitaminosis A in the adult follows the ingestion of massive doses of a vitamin concentrate or food that contains huge quantities of vitamin A. The only known toxic foods are the livers of some fish and of certain Arctic mammals, as polar bears, bearded seals, Greenland fox, and Eskimo huskies. The clinical picture of the acute poisoning in the adult has been described in the section relating to the historical background. Symptoms appear about four to eight hours after ingestion. Headache is the predominant manifestation and was described by two men in Stefánsson's [18] expedition as violent, localized in the forehead and eyes, and as being the worst either of them had ever suffered. Nausea, vomiting, vertigo or giddiness, drowsiness, sluggishness, irritability, an irresistible desire for sleep, and local or generalized peeling of the skin comprise the commonly-reported findings. Complete physical examinations and laboratory studies have not been carried

17. A complete report of this case will be published by Dr. Mary Mulloy.

17a. An identical case has been described by Dr. Jose M. Cluet Garcia, of Barcelona (Acta pediat. españ. **9**:1448, 1951).

18. Stefánsson, V.: The Friendly Arctic, New York, The Macmillan Company, 1932, p. 479.

out. Lonie [19] has reported a family in New Zealand with suspected food poisoning. Careful questioning revealed that the previous meal contained shark liver obtained that day from a fisherman who had caught two sharks. The liver was immediately removed from one of the sharks and eaten about four hours later. Severe headache, dizziness, nausea, and vomiting resulted. Recovery was rapid and complete and, in fact, was succeeded by a remarkable feeling of well-being. Thirty-six hours later there occurred an extensive desquamation of the skin, commencing round the mouth and completed in about a week. In one case the epidermis of the hands came off in an almost complete cast like a glove. One man, aged 47 years, who was partially bald, had a fresh growth of new black hair on the bald crown of his head and the hair elsewhere on his head, previously gray, grew in black. The "rejuvenation" did not last after the first few weeks. It is interesting in this respect that Stefánsson observed a definite increase in the amount and growth of his hair during each Arctic expedition. Vitamin A assay from the liver of the second shark showed 165,000 units per gram. Apparently toxicity through excess vitamin A is not uncommon among New Zealand fishermen who eat hapuka (groper), kingfish, or swordfish liver. Following desquamation, their hands become completely free of the partially-healed indolent type sores which are common among fishermen.

In view of the recent observations of Marie and Sée in infants, it seems plausible to assume that the major symptoms in this group, aside from the skin lesions, are the direct result of increased intracranial pressure. Recovery is rapid. The minimal amount of vitamin A necessary to produce symptoms in the adult is not known, but may be estimated to be in excess of 1,000,000 units.

C. Chronic Hypervitaminosis A

1. *Infant.*—The first case of chronic hypervitaminosis A in childhood was reported by Josephs [10] in 1944. Three years later, Toomey and Morissette [20] described a similar case in an infant, aged 2 years. They reproduced the disease in this child by the administration of 6,200,000 units of vitamin A during a period of 14 days. The preparation used contained a negligible amount of vitamin D. Additional cases have been reported during the past four years.[21] The symptoms appear most frequently in the second or third year of life and are preceded by months of excessive intake of vitamin A. Anorexia, pruritus, and a failure to gain

19. Lonie, T. C.: Excess Vitamin A as a Cause of Food Poisoning, New Zealand M. J. **49**:680, 1950.

20. Toomey, J. A., and Morissette, R. A.: Hypervitaminosis A, Am. J. Dis. Child. **73**:473, 1947.

21. Dickey, L. B., and Bradley, E. J.: Hypervitaminosis A: Case Report, Stanford M. Bull. **6**:345, 1948. Rothman, P. E., and Leon, E. E.: Hypervitaminosis A: Report of 2 Cases in Infants, Radiology **51**:368, 1948. Fried, C. T., and Grand, M. J. H.: Hypervitaminosis A, Am. J. Dis. Child. **79**:475, 1950. Wyatt, T. C.; Carabello, C. A., and Fletcher, M. E.: Hypervitaminosis A: Report of a Case, J. A. M. A. **144**:304, 1950. Bair, G.: Chronic Vitamin A Poisoning: Report of a Case, ibid. **146**:1573, 1951. Naz, J. F., and Edwards, W. M.: Hypervitaminosis A: A Case Report, New England J. Med. **246**:87, 1952. Reyersbach, G. C.; Hanelin, J., and Joplin, R. J.: Vitamin A Intoxication: Report of a Case, ibid. **246**:978, 1952. Case 623, in Case Reports of Children's Memorial Hospital, Chicago, **9**:1831, 1951. Goldzier, S. E.; Pisacano, J. C., and Wald, A. M.: Hypervitaminosis A, J. Pediat. **41**:198, 1952.

in weight are the commonest initial manifestations. Increasing irritability, tender bony swellings, limitation of motion, and resistance to handling subsequently make their appearance. Concomitant with the development of these symptoms, or later, there may occur varying degrees of alopecia, coarseness of the hair, seborrheic-like cutaneous eruptions with or without carotenosis, cracking and bleeding of the mucous membranes of the lips, fissuring at the corners of the mouth, and a hesitant stiff gait. The liver is slightly enlarged. Splenomegaly and clubbing of the fingers, present in Josephs' case, have not been observed by other authors. X-rays of the tender swellings show periosteal reactions, the so-called hyperostoses, greatest in width at or near the mid-shaft and affecting multiple bones. A history of excessive vitamin A ingestion, an increased level of serum vitamin A, and prompt recovery following the elimination of this vitamin from the diet complete the picture.

Two cases of chronic hypervitaminosis A form a connecting link between the acute and the chronic form. In the report by Gribetz and his associates,[22] Case 2, a white girl, aged 17 months, had an enlargement of the head. Pneumoencephalogram and ventriculogram revealed slight dilatation of the ventricles. After the elimination of vitamin A this abnormality became arrested or disappeared. In the second case, a white girl, aged 6½ months, reported by Arena [23] and his associates, showed a marked craniotabes as the predominating symptom. The head measured 47 cm. in circumference and the chest 43 cm. The entire skull was extremely soft, and the area about the anterior fontanelle felt more like a stiff membrane than bone. X-rays of the skull showed thin bones throughout and no hyperostoses. The skull bones became normal after the elimination of all vitamin preparations. It seems reasonable to assume that both children had increased intracranial pressure with resulting hydrocephalus.

2. *Adult.*—There is one case report of chronic hypervitaminosis A in the adult. Sulzberger and Lazar [24] have described a woman, aged 44 years, who complained of excessive loss of hair of two months' duration and generalized migratory bone pains. The duration of menstruation was reduced by three days, the flow lasting five days instead of eight, and it appeared smaller in amount. Pruritus and dryness of the skin with subsequent pigmentation had been present for six months, and fissuring at the corners of the mouth and nasal apertures for five months. During this entire period she experienced night sweats, and her eyes seemed increasingly more prominent. The patient had taken about 600,000 units of vitamin A daily for a period of 18 months, supplemented by doses of 1,000,000 to 2,000,000 units on special occasions, e. g., suspicion of oncoming colds or dry throats. This self-medication was inspired by a radio "nutrition commentator." Within 10 days after discontinuing vitamin therapy, the joint and bone pains disappeared, as did the pruritus and superficial brawny desquamation of the skin. The case differs from the infantile form in the mildness of the bone symptoms and the absence of x-ray changes, the menstrual alterations, the questionable exophthalmos, the pigmentation of the skin, the softness and brittleness of the fingernails, and the night sweats.

22. Gribetz, D.; Silverman, S., and Sobel, A.: Vitamin A Poisoning, Pediatrics **7**:372, 1951.

23. Arena, J. M.; Sarazen, P., and Baylin, C. J.: Hypervitaminosis A, Pediatrics **8**:788, 1951.

24. Sulzberger, M. B., and Lazar, M. P.: Hypervitaminosis A: Report of a Case in an Adult, J. A. M. A. **146**:788, 1951.

It is generally believed that no ill effects occur in cases of carotenosis, although Josephs [10] presents evidence that in severe cases the total serum lipids are elevated and the basal metabolic rate reduced.

II. BIOCHEMISTRY OF VITAMIN A

Before undertaking an evaluation of the symptoms and signs of hypervitaminosis A it seems desirable to present a summary of facts known about the biochemistry of vitamin A and to undertake some interpretations of these facts.

A. Carotene; Source of Vitamin A

Vitamin A is an alicyclic diterpene alcohol with the structure shown in Figure 1. It occurs throughout the animal kingdom as a necessary, but unsynthesizable, compound which must be provided in the diet. Its ultimate source is the plant pigment, carotene, the yellow-orange pigment so familiar in carrots. Carotene is one of the carotenoid pigments occurring in all green plants in association with

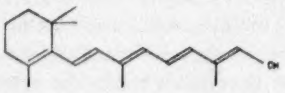


Fig. 1.—All-trans vitamin A.

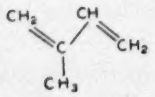


Fig. 2.—Isoprene.

chlorophyll in the chloroplasts of plant cells. Carotene present in small marine plant forms is the ultimate source of vitamin A for marine animals. The carotenoids account for much of the brilliant coloration of fall, when chlorophyll is destroyed in many plant forms.

Carotene is readily synthesized by plants, although the pathway of synthesis is unknown. Suffice it to say that carotene belongs to the abundant group of plant compounds, the terpenes and polyterpenes, which are condensation products of the basic unit, isoprene [25] (Fig. 2).

The exact function of carotene in plants is unknown. Its powerful absorption band for blue-violet light suggests a function similar to that of chlorophyll, namely the utilization of solar energy for a chemical reaction. That it may function as a reducing agent, or antioxidant, is suggested by the fact that the concentration of carotene in leaves decreases on their exposure to sunlight, while that of carotene's oxidation products, the xanthophylls, increases.[26] Thus it may protect certain vital,

25. Willstätter, R., and Stoll, A., cited by Meyer, B. S., and Anderson, D. B.: Plant Physiology, New York, D. Van Nostrand Company, Inc., 1939, pp. 327-328.

26. Karrer, P.: Organic Chemistry, translated by A. J. Mee, New York, Nordeman Publishing Company, Inc., 1938, pp. 651-680.

but readily oxidizable, compounds, such as unsaturated fatty acids, from the action of oxygen which is formed during the over-all reaction of photosynthesis. The structural formulae for β-carotene and for a common plant xanthophyll, zeaxanthin, are shown in Figures 3 and 4 (the all-trans stereoisomers, the most important according to Zechmeister,[27] are shown).

B. Digestion of Carotene and Vitamin A

All animals derive their vitamin A ultimately from plant carotene by (1) the direct conversion of ingested carotene (herbivores), (2) the ingestion of organs, particularly liver, of animals that have accomplished (1) already (carnivores), or (3) a combination of (1) and (2) (omnivores).

Ingested carotene and vitamin A are lipoid in chemical nature and associated with fats in the lumen of the digestive tract. Prior to absorption by the intestinal mucosa these fats are made water-soluble in a two-step process. The first step is enzymatic fission and depends upon the action of intestinal and pancreatic hydro-

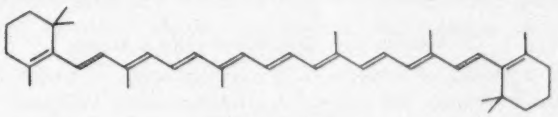


Fig. 3.—β-carotene.

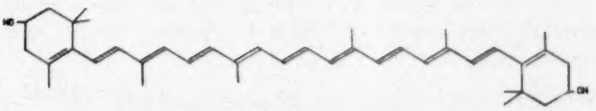


Fig. 4.—Zeaxanthin.

lyzing enzymes. Fatty acids are formed as a result of this fission. The second step is emulsification of these fatty acids and depends upon the formation of complexes with the water-soluble bile salts. In diseases interfering with enzymatic fission, as cystic fibrosis of the pancreas, or with emulsification, as obstructive jaundice, there are steatorrhea and loss of carotene and vitamin A in the feces, occasionally giving rise to vitamin A deficiency. This may be averted to a certain extent by feeding vitamin A dispersed in an aqueous medium.[28]

Carotene is converted to vitamin A principally by the intestinal mucosa. In rats carotene remains unchanged in the lumen of the digestive tract and tends to accumulate in the intestinal wall during absorption. Parenterally-administered carotene accumulates in the liver without conversion to vitamin A.[29] The conver-

27. Zechmeister, L.: Stereoisomeric Provitamins A, in Harris, R. S., and Thimann, K. V., Editors: Vitamins and Hormones: Advances in Research and Applications, Vol. 7, New York, Academic Press, Inc., 1949, pp. 57-81.

28. Sobel, A. E.; Sherman, M.; Lichtblau, J.; Snow, S., and Kramer, B.: Comparison of Vitamin A Liver Storage Following Administration of Vitamin A in Oily and Aqueous Media, J. Nutrition **35**:225, 1948.

29. Sexton, E. L.; Mehl, J. W., and Deuel, H. J., Jr.: Studies on Carotenoid Metabolism: The Relative Provitamin A Activity of Carotene When Introduced Orally and Parenterally in the Rat, J. Nutrition **31**:299, 1946.

sion of carotene is probably not simply hydrolytic, but rather a two-stage oxidation and reduction as follows[30]:

(1) $C_{40}H_{56} + 2O \rightarrow 2\ C_{19}H_{27} \cdot CHO$
Carotene — Vitamin A aldehyde

(2) $2\ C_{19}H_{27} \cdot CHO + 4\ H \rightleftarrows 2\ C_{19}H_{27} \cdot CH_2OH$
Vitamin A alcohol

If the rate of ingestion of carotene exceeds the rate of reaction (1) clinical carotenemia results. The presence of carotenemia in hypothyroidism, in lipoid nephrosis, and in diabetes mellitus suggests some inhibition of this reaction in these diseases.

Reaction (2) is readily reversible in the presence of the appropriate oxidation-reduction system. This reaction apparently occurs in many tissues (see below). It has been shown that vitamin A aldehyde may be substituted for vitamin A in the diet.[31] Vitamin E appears to be a reducing agent for this reaction, since its presence in the intestinal tract increases the efficiency of a given dose of vitamin A.[32]

During absorption vitamin A is esterified probably enzymatically. The reaction is:

(3) Vitamin A + fatty acid → vitamin A ester

Following the ingestion of vitamin A or carotene there is a rise in the plasma vitamin A ester level while the vitamin A alcohol remains constant.[33] The vitamin A ester is transported in the lacteals and larger lymphatic channels to the venous system.[34] In thoracic duct obstruction with chylous ascites the plasma vitamin A level may be zero. Some success in correcting this has been obtained by feeding finely-dispersed aqueous vitamin A which is absorbed directly into the portal venous system.[35]

C. Liver; Storage of Vitamin A

The liver is the great storehouse for vitamin A. The liver of the cod is used widely as a human source of vitamin A. The liver of the polar-bear has so much vitamin A it is toxic to man. In human hypervitaminosis A the liver store is greatly increased, while in vitamin A deficiency it is depleted.

This distribution of vitamin A in the cells of various organs has been studied extensively by Popper,[36] who examined tissues microscopically for fluorescence in

30. Hunter, R. F.: The Conversion of Carotene into Vitamin A, Nature, London **158**:257, 1946.

31. Wendler, N. L.; Rosenblum, C., and Tishler, M.: The Oxidization of β-Carotene, J. Am. Chem. Soc. **72**:234, 1950.

32. Hickman, K. C. D.; Kaley, M. W., and Harris, P. L.: Covitamin Studies: The Sparing Action of Natural Tocopherol Concentrates on Vitamin A, J. Biol. Chem. **152**:303, 1944.

33. Popper, H.; Steigmann, F.; Dubin, A.; Dyniewicz, H. A., and Hesser, F. P.: Significance of Vitamin A-Alcohol and Ester Partitioning Under Normal and Pathologic Circumstances, Proc. Soc. Exper. Biol. & Med. **68**:676, 1948.

34. Coates, M. E.; Thompson, S. Y., and Kon, S. K.: Conversion of Carotene to Vitamin A in the Intestine of the Pig and of the Rat: Transport of Vitamin A by the Lymph, in Proceedings of Biochemical Society, Biochem. J. **46**:xxx, 1950.

35. Gribetz, D., and Kanof, A.: Chylous Ascites in Infancy: With Report of a Case with Vitamin A Absorption Studies, Pediatrics **7**:632, 1951.

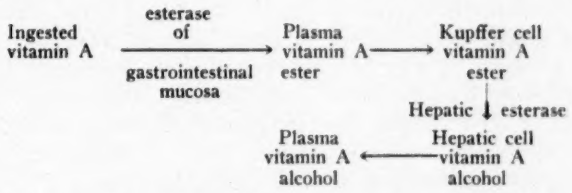
36. Popper, H.: Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, Arch. Path. **31**:766, 1941.

ultraviolet light. Fading green fluorescence indicates the presence of vitamin A. Normal Kupffer cells give a fairly rapidly fading fluorescence from lipoid droplets. This has since been shown to be due to vitamin A esters associated with lipoids (lipoprotein?). The hepatic cells show a similar finding but in addition show a very rapidly fading fluorescence scattered throughout the cytoplasm, which is due to vitamin A alcohol apparently associated with cytoplasmic protein of a water-soluble nature.[37]

It is postulated that Kupffer cell vitamin A ester is converted to hepatic cell vitamin A alcohol by an esterase which probably acts at the lipoid-water interface on the surface of lipoid granules, the reaction being the reverse of reaction (3) above, that is:

(4) Vitamin A ester → vitamin A alcohol + fatty acid

It was further demonstrated that hepatic vitamin A alcohol is in equilibrium with plasma vitamin A alcohol, although this point is debated.[38] It seems definite that ingested vitamin A is esterified, transported to the Kupffer cell for storage in the ester form, and passed on to the hepatic cell as the active alcohol form, the source of plasma vitamin A alcohol. Diagrammatically this may be represented as follows:



In severe infections vitamin A is diminished in the hepatic cell. The hepatic cells show edema, with albuminoid material in the interstitial spaces and sinusoids. Apparently in this circumstance there is a failure of hepatic esterase activity.[36]

In hepatocellular diseases, such as acute hepatitis, decompensated cirrhosis, or severe obstructive jaundice, vitamin A is diminished in both Kupffer and hepatic cells. There is also a flat tolerance curve to ingested vitamin A, suggesting that poor intestinal absorption is the cause for diminished Kupffer cell ester.[36]

There is increased storage of vitamin A in the liver in hypothyroidism and in diabetes mellitus. Whether or not this results from decreased rate of oxidation of vitamin A in the tissues is unknown.[36]

D. Plasma; Circulation of Vitamin A

The normal fasting level of vitamin A in plasma is about 50 γ per 100 cc. This vitamin A has two sources, as noted above. The first source is digested vitamin A, in the ester form, which is transported to the liver (presumably to the Kupffer cell). On feeding vitamin A this fraction rises sharply. The normal fasting level of the ester form in plasma is about 10 γ per 100 cc. The second source of plasma vitamin A is the liver, which supplies vitamin A in the alcohol form (presumably

37. Glover, J.; Goodwin, T. W., and Morton, R. A.: Studies in Vitamin A: Relationship Between Blood Vitamin A Levels and Liver Stores in Rats, Biochem. J. **41**:97, 1947.

38. Ganguly, J.; Krinsky, N. I., and Deuel, H. J., Jr.: Absence of Correlation Between Vitamin A Alcohol in Liver and Plasma in Rats, Federation Proc. **11**:530, 1952.

from the hepatic cell). The level of the alcohol form in plasma is about 40 γ per 100 cc. and does not change with the ingestion of vitamin A. However, in conditions involving decreased hepatic cell vitamin A, e. g., severe infections and liver disease, the plasma vitamin A alcohol level is very low.[39]

Vitamin A is associated in plasma with proteins, the exact nature of which are unknown.[39] In analogy with the conditions in the liver it may be that plasma ester is associated with lipoproteins, while plasma alcohol is associated with a different type of protein. There is some evidence to support this view.[40] Perhaps the abnormal plasma levels of vitamin A found in nephrosis and nephritis result from changes in tissue and plasma proteins.

E. Kidney; Vitamin A in Renal Disease

Normally vitamin A is not present in urine and it is assumed that the normal glomerulus does not excrete vitamin A. There is no available evidence that the kidney participates in regulating the plasma level of vitamin A, except as it metabolizes vitamin A just as other tissues do. However, in the presence of renal disease certain changes may occur in the distribution of the body's vitamin A.

In lipoid nephrosis [41] there is a characteristic rise in plasma vitamin A ester and a marked intolerance to ingested vitamin A. Vitamin A is not found in the urine. One cannot explain these findings by either increased absorption or diminished excretion. However, it may be postulated that the complexes (probably lipoprotein) ordinarily holding vitamin A in the liver (Kupffer cell) are circulating in the plasma, therefore slowing down the transfer of vitamin A ester to the Kupffer cell.[42] This theory is all the more attractive when it is recalled that plasma-protein changes in lipoid nephrosis may be of etiological significance.[43]

In glomerulonephritis, particularly with renal insufficiency, there is a definite increase in plasma vitamin A alcohol, decrease in hepatic cell vitamin A, intolerance to ingested vitamin A, and vitamin A in the urine.[44] It seems unnecessary to postulate that there is renal retention of a substance protecting vitamin A. Although there is no evidence of hepatic damage generally, there is definite evidence of diminished hepatic-cell vitamin A. Perhaps protein-bound vitamin A alcohol is released from hepatic cells to the plasma, in a manner analogous to that postulated for vitamin A ester in nephrosis.

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39. Dzialoszynski, L. M.; Mystkowski, E. M., and Stewart, C. P.: The Mode of Occurrence of Carotene and Vitamin A in Human Blood Plasma, Biochemical J. **39**:63, 1945.

40. Ganguly, J.; Krinsky, N. I.; Mehl, J. W., and Deuel, H. J., Jr.: Studies of the Distribution of Vitamin A as Ester and Alcohol and of Carotenoids in Plasma Proteins of Several Species, Arch. Biochem. **38**:275, 1952.

41. By lipoid nephrosis is meant the pediatric disease entity manifested by hypercholesteremia, hypoalbuminemia, and albuminuria in the absence of hypertension, hematuria, azotemia, or any previous history of renal disease. Reference is not made to the "nephrotic syndrome" encountered in the course of chronic glomerulonephritis.

42. Kagan, B. M.; Thomas, E. M.; Jordan, D. A., and Abt, A. F.: Serum Vitamin A and Total Plasma Lipid Concentrations as Influenced by the Oral Administration of Vitamin A to Children with the Nephrotic Syndrome, J. Clin. Invest. **29**:141, 1950.

43. Lyttle, J. D., and Goettsch, E.: Nephritis and Nephrosis, in Brennemann, Editor: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, Vol. 3, Chap. 6.

44. Footnote 33. Popper, H.; Steigmann, F., and Dyniewicz, H. A.: Plasma Vitamin A Level in Renal Diseases, Am. J. Clin. Path. **15**:272, 1945.

F. Tissue Metabolism of Vitamin A

Probably the most thoroughly-studied site of vitamin A metabolism is the retina.[45] Vitamin A supplied from plasma is utilized for the synthesis of the retinal pigment rhodopsin (visual purple). Rhodopsin is a pink pigment found in the rods of the retina, the receptor cells of dark adaptation. It is composed of carotenoid chromophore groups attached to a lipoprotein base. The synthesis of rhodopsin occurs during darkness. Light waves in the blue-green portion of the visible spectrum (500 mμ) and of low intensity (10^{-6} to 10^{-2} millilamberts) cause a partial decomposition of rhodopsin, with the production of electrochemical energy thus:

Rhodopsin + light energy → retinene + electrochemical energy

In this way radiant energy is converted photochemically to the energy necessary to produce an electrical potential along the optic nerve. In dim illumination retinene may be reconstituted to rhodopsin. In daylight, however, decomposition proceeds to vitamin A, which is lost to the plasma. Therefore a continuous supply of vitamin A must be available and night-blindness occurs with vitamin A deficiency. It is interesting that even the ancient Egyptians were aware of the beneficial effects of liver upon night-blindness.

Another tissue affected to a marked degree by vitamin A is growing bone. Wolbach has summarized this problem well.[46] In vitamin A deficiency epiphysial-cartilage sequences cease before the growth rate of the animal as a whole is diminished. Remodeling of bone also ceases. On the other hand, appositional, or periosteal, bone formation continues. The result of these changes is shortening and thickening of the long bones. The postulate is offered that normally-developing cartilage (organizer or inductor) produces a substance, which causes remodeling of bone (competent tissue). Cellular activity is diminished in vitamin A deficiency, with underproduction of organizer substance, resulting in lack of remodeling. Although the concept of an organizer is interesting, it is adequate to say that some substances such as an enzyme is underproduced.

The effects of vitamin A are more general than those on just retina and bone, however. In vitamin A deficiency changes occur in the epithelium of skin, conjunctiva and cornea, lacrimal glands, salivary glands, pancreas, nasal and paranasal sinus mucosa, tracheobronchial mucosa, and urogenital mucosa. There is a reversion to less differentiated epithelium of squamous cell type with loss of glandular structures, a process called keratinization. Apparently vitamin A is necessary for the formation of glandular secretions. Popper's investigations were interesting in this regard.[36] He demonstrated vitamin A fluorescence associated with lipoid granules in the adrenal cortex (zona fasciculata), ovary (theca cells and follicle cells), testis (Leydig cells and Sertoli cells), lactating breast, and adipose tissue. The exact significance of this is unknown, but it has been shown that virtual castration results from vitamin A deficiency in rats, and that the administration of testosterone prevents this change.[47] This is interpreted by the authors as being possibly due to an interference with the conversion of cholesterol to testosterone in the testis.

45. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A Text in Applied Physiology, Ed. 5, Baltimore, Williams & Wilkins Company, 1950, pp. 1090-1125.

46. Wolbach, S. B.: Vitamin A Deficiency and Excess in Relation to Skeletal Growth, J. Bone & Joint Surg. **29**:171, 1947.

47. Mayer, J., and Truant, A. P.: Effects of Administration of Testosterone on Vitamin A-Deficient Rats, Proc. Soc. Exper. Biol. & Med. **72**:436, 1949.

If we can generalize at all about the effect of vitamin A upon tissues we may say that it acts principally upon cells with active metabolism, particularly those that are secretory in nature. If the above hypotheses are correct, this holds for cartilage and numerous glandular structures. In view of the frequent association of vitamin A with lipids one must consider the possibility that some intracellular element composed at least partly of lipids is instrumental in secretory activity. This may be the mitochondria, or Golgi apparatus, both of which contain large amounts of phospholipids. Since it is known that vitamin A alcohol enters into a reversible oxidation-reduction reaction, namely number (2) above, it may be that it acts intracellularly by preventing oxidation of phospholipids, which contain readily-oxidizable unsaturated fatty acids. In vitro it has been shown that the oxidation of linoleic acid, one of the essential unsaturated fatty acids, is appreciably delayed by the presence of vitamin A.[48]

The vitamin A in the lipoid granules of the adrenal cortex, gonads, and adipose tissue is probably not in the active form, but rather in the inactive ester form, as is the vitamin A stored in the Kupffer cells of the liver.

III. CLINICOCHEMICAL CORRELATION

The findings in hypervitaminosis A may be grouped in the following manner:

A. Chemical alterations
B. Anorexia and nutritional disturbances
C. Cutaneous manifestations
D. Skeletal manifestations
E. Hemorrhagic manifestations
F. Increased intracranial pressure

These are discussed in turn.

A. Chemical Alterations

The body may handle an increasing intake of vitamin A without permanently affecting the plasma level by two mechanisms: (1) increased storage in the liver and (2) increased rate of destruction. However, such enormous intake of vitamin A occasionally occurs that these mechanisms cannot operate rapidly enough, thus producing an increased level in the plasma, and even a slight excretion in the feces and urine. This should not be considered as an impairment of bodily function (e. g., "liver damage"), but rather as an unreasonable demand upon the rate of a physiological response.

Increased liver storage is so great that hepatomegaly may develop. It is not surprising then that the vitamin A tolerance curve is higher and more prolonged than normal, considering the saturation of Kupffer cells with vitamin A that has already occurred. Ultimately most of the vitamin A ester is converted by the hepatic cell to the alcohol form, as evidenced by Gribetz' finding of 67% of the plasma vitamin A in the alcohol form with a fasting total of 675 γ per 100 cc.[22]

Because the plasma vitamin A alcohol level is so very high, it must be concluded that the rate of destruction (oxidation) of vitamin A is slower than the rate of ingestion. It is interesting that one of the early findings of chronic hypervitaminosis

48. Monaghan, B. R., and Schmitt, F. O.: The Effects of Carotene and of Vitamin A on the Oxidation of Linoleic Acid, J. Biol. Chem. **96**:387, 1932.

A is an increase in plasma lipids. This may be interpreted as added evidence that the oxidation of vitamin A is accompanied by the synthesis of lipids and by reduction and conjugation of short chain precursors such as acetate.

B. Anorexia and Failure to Gain Weight

Anorexia is a very nonspecific symptom, and no great effort will be made to explain its origin. Rodahl [49] obtained some experimental evidence that it is a direct result of overdosage. Anorexia is apparently the cause of such secondary findings as failure to gain weight, constipation, hypoproteinemia, and, possibly, anemia. The craving for specific foods high in carotene content is illustrated in Reyersbach's report of a child who was generally anorectic, but, unless prevented, consumed butter in large amounts.

C. Cutaneous Manifestations

Cutaneous manifestations are consistently present. Pruritus is often the initial symptom in the chronic form and may be unusually severe. The origin and mechanism of the pruritus remains unsolved, and one can only speculate whether it is secondary to abnormal intracellular lipid metabolism in the epidermis. Seborrhea and scaling are commonly found. Massive cutaneous hemorrhages around the root sheaths of the hair have been described in the experimental animal, but there is no evidence that this is the explanation for the alopecia in the human chronic forms. Intense subcutaneous hyperemia may be in part responsible for the widespread skin peeling in polar-bear liver poisoning, but again no biopsy studies have been reported. The chloasma-like pigmentation in Sulzberger's patient is unique and without explanation.

D. Skeletal Manifestations

Regularly present in chronic infantile hypervitaminosis A are painful swellings in the extremities usually associated with secondary impairment of locomotor function. These bone lesions and the pruritus are thought to be the cause of the marked irritability. The roentgenological diagnosis depends upon hyperostoses, consistently present in the ulna and metatarsals, often in the clavicle, and less frequently in the humerus, skull, ribs, and femur. The hyperostoses in long bones appear as a periosteal reaction at or near the midshaft, slightly irregular and wavy in outline and tapering off to blend with the cortex towards the diaphysis. The metaphyses and epiphyseal ossification centers are not affected. Caffey [50] has called attention to a zone of diminished density visible between the new periosteal border and the external surface of the old cortex. During the reparative phase following withdrawal of vitamin A, the clear zone disappears, and the hyperostoses shrink and finally fuse with the old cortex. The disappearance of clinical symptoms occurs with great rapidity in contrast to the slow regression of bone changes. A lamellated appearance of some of the hyperostoses during the reparative phase is an infrequent manifestation. Absence of involvement of the mandible has been considered an aid in the diagnosis of this disorder. It was involved in the child described by Rineberg

49. Rodahl, K.: Hypervitaminosis A in the Rat, J. Nutrition **41**:399, 1950.

50. Caffey, J.: Chronic Poisoning Due to Excess Vitamin A: Description of Clinical and Roentgen Manifestations in 7 Infants and Young Children, Pediatrics **5**:672, 1950.

and Gross,[51] and they believed that the patient had concomitant infantile cortical hyperostoses (Smyth-Caffey syndrome). The flurry of interest in a possible relationship between chronic hypervitaminosis A and infantile cortical hyperostoses on the basis of similar x-ray findings has subsided for lack of proof.

Experimental studies by Wolbach [46] have shown that hypervitaminosis A produces acceleration of epiphysial cartilage cell growth and maturation and of the remodeling processes involved in bone growth (accelerated periosteal bone formation in some areas, accelerated resorption with osteoclasis in others). Further studies [52] indicate that this growth effect is mediated independently of the pituitary. In fact, Fell and Mellanby,[53] by growing the bones of fetal mice in tissue culture, were able to demonstrate this vitamin A effect to be a direct one. There was spectacular absorption of bone with loss of the entire bone rudiment with high vitamin A concentrations. If Wolbach's hypothesis that cartilage produces a substance stimulating remodeling of bone is true, then we may suppose that in hypervitaminosis A it is produced in excess causing acceleration of remodeling. It is interesting that the serum alkaline phosphatase, generally considered to be produced by bone, is usually elevated in hypervitaminosis A. Perhaps the intracellular lipids are altered to the extent that enzyme-producing activity is increased. This could be related physiologically to the cutaneous changes.

Renewed interest in the role of scurvy in the development of hypervitaminosis A followed Rodahl's studies [54] in 1949. He repeated Mouriquand's original experiment and found that large doses of vitamin A proved more toxic to guinea pigs given a scorbutic diet than to those given the usual adequate basal diet. Moreover, animals with experimental hypervitaminosis A show low ascorbic acid serum levels and abnormally low contents of ascorbic acid in the adrenals and liver. However, Walker and his associates [55] were unable to demonstrate any protective action of vitamin C when 50 mg. of ascorbic acid was administered daily to rats receiving large doses of vitamin A. In the first case reported by Gribetz, a vitamin C loading test showed an excretion of 66% of the ingested vitamin C in the urine, the normal being at least 40%. It is a known fact that failure in general nutrition per se causes low reserves of vitamin C. This is seen not only in severe infections but in experimental vitamin A deprivation. Chronic hypervitaminosis A also causes a failure in general nutrition, and this may be the explanation for the fragmentary and unsatisfactory evidence of possible coexisting scurvy in some of the case reports. It must be admitted, however, that vitamin C may be affected specifically in hypervitaminosis A, perhaps by chemical destruction during the process of vitamin A oxidation-reduction reactions.

51. Rineberg, I. E., and Gross, R. J.: Hypervitaminosis A with Infantile Cortical Hyperostosis, J. A. M. A. **146**:1222, 1951.

52. Wolbach, S. B., and Maddock, C. L.: Vitamin-A Acceleration of Bone Growth Sequences in Hypophysectomized Rats, A. M. A. Arch. Path. **53**:273, 1952.

53. Fell, H. B., and Mellanby, E.: Effects of Hypervitaminosis A on Foetal Mouse Bones Cultivated in Vitro: Preliminary Communication, Brit. M. J. **2**:535, 1950.

54. Rodahl, K.: Hypervitaminosis A and Scurvy, Nature, London **164**:531, 1949.

55. Walker, S. E.; Eylenburg, E., and Moore, T.: The Action of Vitamin K in Hypervitaminosis A, Biochem. J. **41**:575, 1947.

E. Hemorrhagic Manifestations

In the experimental animal hemorrhages and bony fractures form the outstanding characteristics of vitamin A overdosage, and death from bleeding in the absence of trauma is a common occurrence. The hemorrhages are so widespread that on histologic examination other changes are often obscured. In 1944, Light, Alscher and Frey [56] presented evidence that a pronounced hypoprothrombinemia constitutes the mechanism responsible for the spontaneous hemorrhages. Doses of approximately 5,000 units of vitamin A per day produced a demonstrable hypoprothrombinemia in white rats within a period of 10 days. Both the alcohol and the ester form have had equal effect on the prothrombin level, but huge doses of carotene were without effect. They demonstrated that this phenomenon can be controlled by the simultaneous daily administration of 25 γ of vitamin K. There was no evidence that vitamin K prevented or influenced any of the other manifestations of hypervitaminosis A. Walker, Eylenburg and Moore [55] confirmed these studies and postulated the following explanations: (1) excessive amounts of vitamin A might increase the rat's demand for vitamin K; (2) it might interfere with the synthesis or absorption of vitamin K; (3) it might cause destruction or inactivation of vitamin K within the liver or elsewhere in the body. The second of these hypotheses is probably the correct one. It is possible that vitamin A inhibits the bacterial synthesis of the chemically-related vitamin K. Manifestations of bleeding in humans with hypervitaminosis A have been relatively insignificant. Epistaxis has been described in many of the case reports, but it is, of course, a frequent occurrence in normal children. Bleeding from the fissures of the lips has been trivial. The posttonsillectomy hemorrhage in Josephs' case may or may not have been incidental. In Toomey's case the stools were dark and tarry and contained fresh blood. In this patient the platelet counts were normal; bleeding time, 4½ minutes; clotting time, 3 to 4 minutes; prothrombin time, 30 seconds (control, 29 seconds). In the first case described by Gribetz the bleeding, clotting, and prothrombin time were within normal limits. The subdural hematoma in Berrey's [57] case was probably an unrelated incidental finding, as there was no other evidence of bleeding and no abnormality in the blood-clotting mechanism. No hemorrhagic lesions have been described in the acute form in infants or adults.

F. Increased Intracranial Pressure

Evidence that vitamin A poisoning produces increased cerebrospinal fluid pressure is based on the case reports of infants with bulging fontanelles, the symptomatology that follows the ingestion of polar-bear liver, and the enlargement of the head in the patients described by Gribetz and by Arena. This may be the explanation for the exophthalmos that was consistently produced in rats by Lewis and Cohlan [58] with massive doses of vitamin A in an aqueous preparation. Although

56. Light, R. R.; Alscher, R. P., and Frey, C. N.: Vitamin A Toxicity and Hypoprothrombinemia, Science **100**:225, 1944.

57. Berrey, B. H.: Postinfantile Cortical Hyperostosis with Subdural Hematoma: Report of a Case and Review of the Literature, Pediatrics **6**:78, 1950.

58. Lewis, J. M., and Cohlan, S. Q.: Comparative Toxicity of Aqueous and Oily Preparations of Vitamin A, Pediatrics **9**:589, 1952.

the cause of this phenomenon remains an enigma, the choroid plexus probably produces cerebrospinal fluid at an accelerated rate—another sign of increased cellular activity.

G. Other Comments

There is no evidence that hypervitaminosis A affects the function of the adrenal, gonads (hypomenorrhea of the adult case is difficult to evaluate), adipose tissue, endocrine glands, or retina.

The question of latent or subclinical hypervitaminosis A and the possible existence of mild forms of this disorder deserves consideration. In view of Josephs' observations, a rise in serum lipids may precede any clinical manifestations of vitamin A excess and might help provide a means of diagnosis of a possible latent chronic form. Moreover, pediatricians and internists are frequently confronted with patients who have unexplained bone and joint pain, headaches, pruritus, dryness of the skin, anorexia, and failure to gain in weight. The association of these symptoms with elevated serum vitamin A levels may reveal mild forms of this disorder.

Finally, no information is available concerning possible injury to the fetus as the result of administration of excessive doses of vitamin A during the early months of pregnancy. Realization that the critical period for injury may be only a matter of a few hours suggests the need for experimental work on this subject.

436 N. Roxbury Dr. (Dr. Rothman).

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

ULTIMATE SITE OF SKELETAL DEPOSITION OF STRONTIUM AND LEAD. NORMAN S. MCDONALD, FLORITA EZMIRLIAN, PATRICIA SPAIN, and CLARA MCARTHUR, J. Biol. Chem. **189**:387 (March) 1951.

Careful consideration of the x-ray defraction patterns of the bone ash of rats receiving repeated injections of strontium chloride and lead acetate indicated that both these substances ultimately enter into the internal structure of the inorganic salt crystallites of the bone. Although the evidence presented by the authors gives no information on the initial phase by which strontium and lead are accumulated in bone, it was concluded that these metals ultimately become an integral part of the crystalline structure.

FORBES, Dallas, Texas.

STUDIES TO DETERMINE THE NATURE OF THE DAMAGE TO THE NUTRITIVE VALUE OF SOME VEGETABLE OILS FROM HEAT POLYMERIZATION: I. THE RELATION OF AUTOXIDATION TO DECREASE IN THE NUTRITIONAL VALUE OF HEATED LINSEED OIL. EARLE W. CRAMPTON, R. H. COMMON, FLORENCE A. FARMER, F. MARION BERRYHILL, and L. WISEBLATT, J. Nutrition **43**:533 (April 10) 1951.

The results of these experiments show that peroxidation of polymerized linseed oil is not concerned in the development of any toxic factor and that a lack of vitamin E is not involved in the growth inhibition resulting from the ingestion of heated oil.

FREDEEN, Kansas City, Mo.

NITROGEN RETAINED BY SIX ADOLESCENT GIRLS FROM TWO LEVELS OF INTAKE. FRANCES A. JOHNSTON and DORETTA SCHLAPHOFF, J. Nutrition **45**:463 (Dec. 10) 1951.

Six girls between 13 and 14 years of age were the subjects of this experiment. The mean daily nitrogen intake for the six subjects was 12.20 and 13.97 gm. for the first and second periods, respectively. The nitrogen content corresponded to a mean protein intake of 76.2 gm. in the first period and 87.3 gm. in the second. The mean daily amount of nitrogen retained by all subjects in the first period was 1.42 gm., and during the second period was 2.17 gm. When reduced to units of body size, the mean daily retention was 0.97 gm. per square meter or 29.9 mg. per kilogram during the first period and 1.45 gm. per square meter or 43.7 mg. per kilogram during the second period. This is an increase in the amount retained of approximately 53%, which is large after an increase of only 15% in the nitrogen intake and 6% in the caloric intake. The percentage of the intake of nitrogen retained rose from a mean of 11.6 in the first period to 15.4 in the second. The mean intake of 76.2 gm. of protein per day was probably adequate for these subjects. The intake of 87.3 gm. of protein was undoubtedly more than adequate.

FREDEEN, Kansas City, Mo.

THE EFFECT OF FAT LEVEL OF THE DIET ON GENERAL NUTRITION: VIII. THE ESSENTIAL FATTY ACID CONTENT OF MARGARINES, SHORTENINGS, BUTTERS, AND COTTONSEED OIL AS DETERMINED BY A NEW BIOLOGICAL ASSAY METHOD. HARRY J. DEUEL JR., SAMUEL M. GREENBERG, LILLA ANISFELD and DANIEL MELNICK, J. Nutrition **45**:535 (Dec. 10) 1951.

The authors' results demonstrate that hydrogenated fats contain a surprisingly high proportion of biologically active polyunsaturated acids. There is a semiquantitative relationship between the dosage of hydrogenated coconut oil and its growth-depressing effects. This deleterious action can be overcome when adequate amounts of linoleate are available. The regression of the symptoms occurs progressively as the linoleate dosage is increased from 5 to 50 mg., at which

point there is no evidence of a depressing effect of hydrogenated coconut oil on growth, even when fed at a 500-mg. dosage. The optimum level of linoleate required by fat-depleted male rats would seem to exceed 200 mg. per day. Apparently the requirement of essential fatty acids is increased with the concomitant ingestion of fat. FREDEEN, Kansas City, Mo.

STUDIES ON THE INTERRELATIONSHIP BETWEEN METHIONINE AND VITAMIN B_6. H. J. DEBEY, ESMOND E. SNELL and C. A. BAUMANN, J. Nutrition **46**:203 (Feb. 11) 1952.

The fact that methionine intensifies the effects of vitamin B_6 deficiency suggests that either the amino acid itself or one of its metabolites is harmful to the deficient rat. The levels of methionine in the liver were not altered in vitamin B_6 deficiency, nor did vitamin B_6 increase the rate of removal of methionine from the blood. Homocystine consistently suppressed growth, although not always as effectively as methionine itself. Cystine itself was not particularly harmful to the deficient rat. It was suggested that possibly the harmful metabolite of methionine may still contain the methyl group. The good growth of rats fed pyridoxal or pyridoxamine in diets high in methionine adds another illustration to those in which these forms of vitamin B_6 are at least equal to pyridoxine with respect to producing growth responses in higher animals.

FREDEEN, Kansas City, Mo.

THE RELATIVE UTILIZATION OF ALPHA-TOCOPHEROL AND ALPHA-TOCOPHERYL ACETATE BY HUMANS. ERLING F. WEEK, FRANK J. SEVIGNE and MARIE E. ELLIS, J. Nutrition **46**:353 (March 10) 1952.

The utilization of the free α-tocopherol was found to be significantly superior to the utilization of the α-tocopheryl ester.

FREDEEN, Kansas City, Mo.

AN ATTEMPT TO PRODUCE HEMOCHROMATOSIS EXPERIMENTALLY AND THE EFFECT OF HIGH LEVELS OF COPPER AND CHOLINE IN THE DIET. NATHAN KAUFMAN, J. A. CARTAYA, PHILIP L. WHITE, D. MARK HEGSTED and THOMAS D. KINNEY, J. Nutrition **46**:433 (April 10) 1952.

The present experiments did not produce in the animals a condition closely resembling hemochromatosis. The increase in liver iron which accompanies copper poisoning can be most easily explained as the result of the loss in weight suffered by the animals. It is concluded that choline increases either the absorption or the deposition, or both, of copper, or inhibits its excretion. Copper and choline feeding also increases the level of liver iron and decreases the level of liver fat secondary to weight loss.

FREDEEN, Kansas City, Mo.

TOCOPHEROL CONTENT OF HUMAN MILK AND OF COWS' MILK PRODUCTS USED FOR INFANT FEEDING. PHILIP L. HARRIS, MARY L. QUAIFE and PATRICIA O'GRADY, J. Nutrition **46**:459 (April 10) 1952.

The tocopherol content of human milk was (mean) 0.24 mg. per 100 ml. or about 80 γ per gram of fat; evaporated cows' milk and whole milk powder contained 23 to 40 γ per gram of fat; and proprietary infant foods, 29 to 171 γ of α-tocopherol per gram of fat.

FREDEEN, Kansas City, Mo.

CHANGES IN NUTRITIONAL REQUIREMENTS ACCOMPANYING MARKED CHANGES IN HORMONE LEVELS. JOSEPH MEITES, Metabolism **1**:58 (Jan.) 1952.

The object of the study was to determine whether growth retardation produced by administration of hormonal substances to immature rats could be counteracted by administration of supplementary food substances. Growth retardation produced by large doses of diethylstilbestrol or thyroprotein was partially counteracted by administration of vitamin B_{12}. However, this supplement did not affect the decrease in testicular weight brought about by hyperestrinism or hyperthyroidism or the increase in weight of the seminal vesicles produced by the estrogen.

Procaine penicillin and neomycin sulfate completely reversed the growth retardation produced by thyroprotein, but the increased basal oxygen consumption was not affected. Streptomycin was without effect either on growth or on basal oxygen consumption in these circumstances.

Evidence is presented which suggests that vitamin B_{12} may be able to counteract partially the effects of thyroparathyroidectomy as well as the growth retardation (and hair-growth retardation) produced by cortisone administration.

KAPLAN, Cincinnati.

THE IRON CONTENT OF MOTHER'S MILK AND THE RESPONSE TO IRON ADMINISTRATION. W. NEUWEILER, Schweiz. med. Wchnschr. **15**:396 (April 12) 1952.

The iron content of the mother's serum and her milk was determined by the method of Heilmeyer and Ploetner. The milk iron varied from 7 to 141 γ per 100 cc. The highest values were obtained on the eighth day post partum. There was no parallelism with the serum iron. A ferrous salt was given by mouth. In two of six cases, the iron of the milk increased above the error of the method. Intravenous administration of a ferric salt did not result in an increase of the milk iron, although the serum iron was increased considerably. It appears that the mechanism of iron transfer from blood to milk is not simple.

AMBERG, Rochester, Minn.

NUTRITION AND ITS EFFECTS ON SOMATIC DEVELOPMENT IN SCHOOL CHILDREN. RICARDO G. GONZALEZ, Acta pediat. españ. **101**:610 (May) 1951.

Dr. Gonzales says that although heredity has much to do with the growth and development of children, the big factor which all physicians can help control is nutrition. Poor nutrition can be responsible for many serious somatic defects and for poorer learning capacity; many potentially healthy children grow up with serious defects. The author describes physical defects found in poor nutrition by system, muscular, skeletal, etc., and also studies done to show lowered hemoglobin, lowered metabolic rates and poorer results in intelligence and performance tests. These children also showed inferior anthropomorphic measurement as compared with well-fed children in the same geographical area. Naturally, in the children examined there was a study of the quality and quantity of food consumed daily. This was checked by consultations with parents.

The author believes that education of parents and children, better economic conditions, and properly managed school lunch programs will help.

ALLEN, San Francisco.

DETERMINATION OF THE ELECTROLYTES IN ACUTE NUTRITIONAL DISTURBANCES. OSCAR CORREA B. Y ANDRES DEL VALLE, Rev. chilena pediat. **23**:66 (Feb.) 1952.

A study of electrolyte concentration in acute nutritional disturbances is carried out. The work comprised sodium, chloride, potassium, and bicarbonate determinations on 25 infants suffering from dyspepsia or toxicosis, 16 of them in a group in which the electrolyte figures provided a criterion for replacement treatment and 9 in another group, taken as control. As replacement therapy Ringer, Hartmann, Darrow, and glucose solutions were used.

Sodium analysis on admission of 24 infants revealed decreased levels in 19, high in 3, and normal in 2. A close relation was not seen between deficiency of this electrolyte and dehydration. Of 25 patients 22 had acidosis, with bicarbonate figures lower than 23 mEq., and 3 had normal acid-base balance. Infants affected with toxicosis showed the highest electrolyte deficits. In the first group, except three patients who died, all had a complete recovery from dehydration in a period of about five days, and in the second group, excluding two fatalities, eight days elapsed before the same result was seen in three patients. Attempts to restore potassium losses by Darrow's solution did not have striking results.

FROM THE AUTHOR'S SUMMARY.

IS IT PERMISSIBLE TO NURSE AN INFANT IN THE PRESENCE OF PUERPERAL MASTITIS? HANS CZERMAK, Med. Klin. **47**:404 (March 28) 1952.

It is permissible to nurse an infant in the presence of puerperal mastitis. With exception of the rare severe Streptococcus mastitis, the infant is to be put to the diseased breast. When the mastitis has progressed, the breast is to be emptied mechanically until incised. The milk

so obtained is boiled before feeding. It is emphasized that a breast in full lactation should not, and cannot, be put at rest. In the prophylaxis and in the management of mastitis, the importance of specially trained nurses is strongly stressed.

AMBERG, Rochester, Minn.

ANOXIA IN INFANTILE DEHYDRATION. E. KERPEL-FRONIUS, F. VARGA, J. VONOCZKY, and K. KUN, Acta paediat. **40**:10 (Jan.) 1951.

The balance between oxygen transported to the tissues and oxygen consumption was studied in 10 dehydrated and 5 normal infants. The obtained data were compared to the arteriovenous oxygen difference found in each case.

The amount of oxygen supplied to the tissues (cardiac output times volume per cent of arterial oxygen) was found to decrease parallel with increasing dehydration. The decrease in oxygen supply is caused by an enormous fall in cardiac output. The ever-progressing narrowing between oxygen demand and supply results in a condition of anoxia of the stagnating type comparable in its extent with conditions described in traumatic shock.

Anoxia in dehydration is aggravated by every factor capable of increasing the call of tissues for oxygen because dehydration—i. e., anhydremia—prevents adjustment of circulation to higher metabolic needs. Thus, fever, restlessness of the patient, or a diet rich in proteins may induce anoxia at relatively mild stages of dehydration. The most dangerous complication of dehydration is pneumonia. There are simultaneous lowering of the arterial oxygen load and a decreased cardiac output. On the other hand, oxygen demand is increased by fever. In severely dehydrated patients, without fever, oxygen consumption decreases significantly.

The treatment of anoxia in dehydration should aim at the correction of disparity between oxygen supply and demand. Cardiac output is raised by correcting anhydremic circulatory failure. At the same time the oxygen demand of the tissues has to be brought down to basal levels by treatment of fever, infection, and restlessness and by avoidance of proteins.

FROM THE AUTHORS' SUMMARY.

Vitamins; Avitaminoses

SCORBUTIC ARTHROPATHY IN THE GUINEA PIG. CONRAD L. PIRANI, CHAUNCY G. BLY, and KENNETH SUTHERLAND, Arch. Path. **49**:710 (June) 1950.

The articular lesions of acute and chronic scurvy were studied in 82 guinea pigs. Scorbutic arthropathy involved in different degrees all the joints of the body. It was characterized by hemorrhages and fibroblastic proliferation, minor changes of the articular cartilage and striking absence of inflammatory cells. Hemorrhages and mechanical stress are the all-important factors in determining the general picture of scorbutic arthropathy. The incidence and the severity of the hemorrhagic manifestations declined considerably as chronic scurvy advanced. Spontaneous improvement of the intra-articular lesions (true ankylosis) also occurred. Periarticular lesions (pseudoankylosis) were less likely to improve spontaneously or even after therapy. Under the conditions of the experiment the periarticular appeared to be, for the most part, irreversible and responsible for the persistent functional impairment. The authors believe that there is only a superficial morphological similarity between the articular lesions of scurvy and those of either rheumatoid arthritis or rheumatic fever. It is possible, however, that partial ascorbic acid deficiency may be a predisposing or a contributing factor in certain forms of human arthritis.

HAW CHAN, San Francisco.

DEPOSITION OF B VITAMINS IN NORMALLY DEVELOPING FETUSES AS EVIDENCE FOR INCREASED VITAMIN NEEDS OF THE RAT FOR REPRODUCTION: I. THIAMINE AND RIBOFLAVIN. MARGARET BARRETT and GLADYS EVERSON, J. Nutrition **45**:493 (Dec. 10) 1951.

Barrett and Everson found that prior to the 16th day of pregnancy in the rat there is apparently only a minor need for thiamine and riboflavin beyond the amount recognized as being necessary for the nonpregnant adult animal. Fetal growth in the rat is small during the first

half of pregnancy; it becomes exceedingly rapid in normal litters from the 18th day of the gestation period to parturition. This accelerated synthesis of new tissues increases the thiamine and riboflavin needs of the mother considerably. The development of the placenta itself imposes a very minor need for thiamine and riboflavin.

FREDEEN, Kansas City, Mo.

THE EFFECT OF VITAMIN B_{12} ON REPRODUCTION AND LACTATION IN RATS RECEIVING PORK OR BEEF DIETS. MARIAN L. MEYER, H. T. THOMPSON and C. A. ELVEHJEM, J. Nutrition **45**:551 (Dec. 10) 1951.

Meyer and associates concluded that the difficulty, in reproduction and lactation often associated with a roast pork diet for rats, has not been eliminated. Oral supplements of crystalline vitamin B_{12} at the 0.1 γ per day level did not overcome the lactation failure frequently seen in rats fed roast pork as the sole source of protein but did help in overcoming the conception lag often accompanying such a diet. Addition of a methanol liver extract (0.05 γ B_{12} per day) did not affect the lactation performance of animals on the pork diet. Substitution of dextrin for sucrose caused lactation failure in every group. Addition of 5 mg. streptomycin per 100 cc. did not produce any improvement in the lactation of the pork-fed animals. Rat milk has a high vitamin B_{12} activity (average about 20 γ per milliliter). The vitamin B_{12} level of the milk seemed to follow the reproduction and lactation performance regardless of the level of the vitamin in the diet.

FREDEEN, Kansas City, Mo.

EFFECT OF AUREOMYCIN AND PENICILLIN UPON THE VITAMIN REQUIREMENTS OF THE RAT. H. E. SAUBERLICH, J. Nutrition **46**:99 (Jan. 10) 1952.

The inclusion of penicillin or aureomycin in the completely vitamin-supplemented basal diet had no effect upon the growth of the animals. The addition of penicillin to the diet (0.01%) caused a marked stimulation in the growth of rats fed diets free of or low in thiamine, pyridoxine, pantothenic acid, and, to some extent, riboflavin. Aureomycin (0.01%) had a similar effect in the case of pantothenic acid and thiamine deficiencies.

FREDEEN, Kansas City, Mo.

STUDIES ON THE EFFECT OF ATABRINE ON VITAMIN A METABOLISM. K. GUGGENHEIM, J. Nutrition **46**:141 (Feb. 11) 1952.

Atabrine added to a diet containing 50% skim milk powder at a level of 800 mg. per kilogram of ration does not impair the utilization of food by the rat, if adequate supplements of vitamin A are also given. Guggenheim showed that prolonged administration of quinacrine exerts a profound effect on the metabolism of vitamin A. Quinacrine damages the liver, impairing its ability to store vitamin A and thus depriving the animal of its relative independence of variations in the supply of the vitamin obtained from its food. It seems to depress the absorption rate of vitamin A and of carotene. After the administration of the provitamin, vitamin A could be detected in the intestinal wall; this confirms earlier work that the conversion of carotene into vitamin A takes place in the intestinal wall. The vitamin A requirement does not appear to be affected by quinacrine.

FREDEEN, Kansas City, Mo.

RELATIONSHIPS BETWEEN INTAKE AND SERUM LEVELS OF ASCORBIC ACID, VITAMIN A, AND CAROTENE OF SELECTED GROUPS OF CHILDREN WITH PHYSICAL SIGNS OF VITAMIN DEFICIENCIES. SUSAN B. MERROW, R. F. KRAUSE, J. H. BROWE, C. A. NEWHALL and H. B. PIERCE, J. Nutrition **46**:445 (April 10) 1952.

This interesting three-year study made on school children showed that the nutrient intakes of ascorbic acid, total vitamin A, and carotene reflect serum levels of ascorbic acid, vitamin A, and carotene, respectively, and vice versa.

FREDEEN, Kansas City, Mo.

SCURVY IN MENTALLY DEFECTIVE CHILDREN. D. W. BEYNON and P. R. EVANS, Great Ormond St. J. (No. 2) 90 (Dec.) 1951.

Of 10 cases of scurvy seen in a period of two and one-half years, 6 were in mentally defective children who refused normal diet. Onset of scurvy was later than in the usual infant. All were grossly underweight, though no other vitamin deficiency was noted.

McGUIGAN, Evanston, Ill.

CONGENITAL VITAMIN DEFICIENCY. M. L. KUNDU, J. Indian M. A. **16**:350 (July) 1947.

Kundu describes a syndrome of chronic intestinal disorder with signs and symptoms of both celiac disease and rickets but not conforming to the usual picture of either. He believes that this condition occurs mainly in cases in which a mother has had repeated pregnancies at short intervals, with a resultant vitamin A and D deficiency which is transmitted to the infant. He pleads for better education to prevent such frequent pregnancies.

McGUIGAN, Evanston, Ill.

Hygiene; Growth and Nutrition; Public Health

THE STATE OF ILLINOIS COOPERATES WITH THE OPHTHALMOLOGIST AND OTOLARYNGOLOGIST. HERBERT R. KOBES, Illinois M. J. **99**:303 (June) 1951.

Kobes points out that many children in Illinois with hearing difficulties have needed help through medical facilities. Private physicians, school health programs, the hospitals, the Division of Services for Crippled Children, the Department of Public Welfare through the School for the Deaf, the Division of Education for Exceptional Children and the Division of Vocational Rehabilitation give through their combined resources programs which are probably not excelled.

Since its inception the Illinois program for the child with hearing loss has been developed from the "Syllabus on Hearing Conservation" of the Academy of Ophthalmology and Otolaryngology. From the family physician, often through the health department, the cases are referred to the Division of Services for Crippled Children for further evaluation and planning for future care.

The Division's clinics are held in about 40 different communities throughout the state. Here the child is seen by a pediatrician and a speech and hearing consultant. If a patient is found to have a loss of 20 or more decibels in two or more frequencies in the same ear, the patient is referred to an otologist certified by the American Board of Otolaryngology for definitive medical diagnosis and plan of treatment at the clinic; a public health nurse or medical social worker may aid in interpreting to the family what may need to be done for the child. The otologist reports his findings to the division. Office treatments, hospital care for surgery, hearing aids and training in their use, school seating placements, and lip reading instruction are among the recommendations that are made. Through the resources of the Division for Crippled Children all children at the School for the Deaf who should have hearing aids to develop their educational program to the fullest extent are able to obtain aids. This has resulted in graduating a considerable number of children from this residential school to schools in their own home community—even the regular classrooms.

Efforts are directed toward educating physicians, public health workers, and the lay public to the need of making the earliest possible diagnosis in children born with a severe hearing loss or deafness. Under this educational program during the past five years more and more preschool deaf children are found annually, and the long tedious program of training and education is begun for the children and their parents. Mothers and their children aged from 2 to 5 years come to Jacksonville for 10 days to the annual Institute for Mothers of Pre-School Deaf Children. Lectures by authorities in child care and the medical and education problems of the deaf are combined with demonstrations concerning the training that needs to be followed to gain speech for many of these children.

This program has been carried out for four years. It has become evident that there is need for medically trained men with training in lip or speech reading, in acoustical training, and in

hearing-aid fitting. Courses teaching the elements of complete rehabilitation in this field are available on a postgraduate level. During the past summer some 30 public health nurses had an intensive two-week course in hearing testing to fit them into community conservation of hearing programs. Courses are offered at various universities in the training of teachers of the deaf and hard of hearing. In the educational institutions concerned with training of handicapped children, one frequently finds severe social and educational impairment which becomes relieved when a further diagnostic evaluation reveals a second disorder and thus makes possible a different educational program for the child. The visually handicapped child who does poorly in the sight-saving class may have a serious hearing loss, too.

BARBOUR, Peoria, Ill.

OBSERVATIONS ON AFRICAN CHILDREN. E. A. BEET, Arch. Dis. Childhood **26**:127 (April) 1951.

An account is given of the findings of a health survey carried out among the Lala tribe of Northern Rhodesia, preceded by a short description of the country they live in and the diet on which they subsist. The results of the survey are recorded in tables, and a brief description is given of the clinical signs found, particularly those connected with malnutrition.

It is concluded that Lala children show clinical evidence of a diet deficient in calories, protein, vitamins A, B complex and C, and iodine.

It is considered that kaffir corn is at least as good a staple as finger millet, and that a change from finger millet to kaffir corn is justified in an effort to preserve the forest areas which are doomed to destruction if the cultivation of finger millet on the present system is allowed to continue.

KELLY, Milwaukee.

PERINATAL MORTALITY AND INFANT MORTALITY IN URUGUAY. JULIO A. BAUZÁ, Bol. Inst. internac. am. protec. infancia **26**:27 (March) 1952.

The author states that perinatal mortality establishes the danger of the fetus during the period of its life from the 28 weeks of gestation to the end of the first month after birth. Knowing it, one can determine natimortality—excluding abortions and fetal deaths of less than 28 weeks of gestation—relating it to the total of births per year, thus obtaining the natimortality per 1,000 live births.

The natimortality is moderate in Uruguay, 26 per 1,000 live births, having been greatly lowered in the last ten years. Early neonatal mortality comprises the deaths occurring in the first week of life, and late neonatal mortality the deaths from 7 to 30 days of life. The first is 55% of the mortality of the first month and its rate per 1,000 live births is 12. It is due principally to prematurity and injuries at birth and to the group of diseases pertaining to the first year of life.

The mortality in the first day of life reaches 4 per 1,000 live births. Syphilis causes a very reduced number of neonatal deaths. Late neonatal mortality is due particularly to prematurity, 30% of cases, and to the disease of the respiratory and alimentary tracts. The rate of late neonatal mortality was 10 per 1,000 live births in 1948.

Total neonatal mortality had a rate of 22 per 1,000 live births in 1938. This number has not been reduced in recent years.

The perinatal mortality rate is obtained by adding infant mortality rates and neonatal mortality rates; thus the rate of 49 per 1,000 live births is obtained for the year 1948. The author considers that this rate represents a moderate perinatal mortality and that it can be reduced to 30 per 1,000 by means of better prenatal, neonatal, and after-birth care.

In recent years there have been great advances in the reduction of infant mortality, the rates of which have decreased 50% in comparison with those of 20 years ago. At present infant mortality is 50 per 1,000 live births. In Montevideo the lowest rate was in 1946, with 48.7 per 1,000 live births; there was a slight increase in the three subsequent years. The mortality of the first month is 40% of the mortality for the first year. In the second month a marked decrease can be observed, followed by a new rise in the third month. After this the descent is progressive.

Infant mortality (below 1 year) is still caused chiefly by the diseases of the alimentary tract, followed by prematurity, congenital weakness, and the diseases of the respiratory tract.

Maternal mortality rates are rather low, 2 per 1,000 births. In the city of Montevideo 34.5% of all child births are taken care of at the public health maternity facilities and 5% are attended by the child birth home care facilities of the Department of State.

There are 243 beds for child birth in Montevideo and 383 in the rest of the country. The average of mothers assisted in government establishments in 1950 was 25 per bed in Montevideo and 46 per bed in Salto. In some departments of the interior the percentage is very low, 7 to 15 per bed and per year.

The author proposes that a committee of experts be appointed to study the data presented by the various American countries and propose methods considered most appropriate to reduce perinatal mortality.

FROM THE AUTHOR'S SUMMARY.

Prematurity and Congenital Deformities

ETIOLOGY OF CONGENITAL MALFORMATION. I. GUBERN SALISACHS, Arch. pediat. **2**:123 (Sept.) 1950.

Dr. Salisachs reviews the literature on congenital defects and cites many of the conclusions drawn by Warkany in his monograph in *Advances in Pediatrics* (**2**:1, 1947).

He says that although Warkany describes the factors capable of causing malformations, he does not mention psychosomatic factors. The impact of the latter factors is becoming more and more obvious, although it cannot be measured in any way now available.

Phenocopies are defects which simulate hereditary defects but are due to intrauterine injury at the time of greatest tissue differentiation. Examples of phenocopy and cuts identical with Warkany's in some cases and similar in others, are included. The ability of an abnormal gene to stimulate an organizer and give multiple deformities is called pleiotropia. These variations along with the better-known mechanisms of inheritance make for very complicated problems concerning whether a defect is genetic or environmental.

The factors which may affect the embryo in its early development include (1) infections, (2) toxins, (3) radiations, (4) nutritional defects, (5) endocrine defects, including diabetes and thyroid defects, and (6) mechanical defects.

He quotes Marañon's three laws regarding congenital defects, that (1) defects are rarely seen singly, (2) hereditary mutations change from one generation to another, and (3) the inheritance of certain defects is sometimes equally distributed among offspring.

Dr. Salisachs adds a fourth law, which could be called the embryological chronology of defects acquired during intrauterine life. He has observed in children congenital heart defects and abnormal external auricle of the ear associated with injury or illness during the fourth month of pregnancy, at the time when the development of these parts begins in the embryo.

The author says that we may have to change our attitude toward some of the beliefs held for years by the uneducated. Their truth may be confirmed by a knowledge of the place of the hypophysis in the body economy and the effect of emotions on the humoral or endocrine chemistry. The author cites a number of cases and gives illustrations of congenital defects which may have no explanation unless it be a psychosomatic one. ALLEN, San Francisco.

METHYLENE BLUE IN THE TREATMENT OF METHEMOGLOBINEMIA IN PREMATURE INFANTS CAUSED BY MARKING INK. JAMES N. ETTELDORF, J. Pediat. **38**:24 (Feb.) 1951.

Methylene blue, 1.5 mg. per kilogram, in a 0.1% solution, given intravenously, promptly relieved cyanosis in eight infants with methemoglobinemia. The disorder had been caused by aniline-containing ink used in marking diapers.

MACDONALD, Pittsburgh.

FEEDING OF PREMATURE INFANTS: VALUE OF HIGH CALORIC DIETS IN REDUCING THE LENGTH OF HOSPITAL STAY. JANET B. HARDY and EUGENE O. GOLDSTEIN, J. Pediat. **38**:154 (Feb.) 1951.

Hardy and Goldstein report that premature infants fed on a demand schedule, after the second day of life, will gain weight faster than infants fed by calculated schedule. Infants fed on demand were given cautiously increased amount of formula to the point of tolerance. No ill effects were observed.

MACDONALD, Pittsburgh.

SITUS INVERSUS. NATALIA TANNER-CAIN and E. PERRY CRUMP, J. Pediat. **38**:199 (Feb.) 1951.

Situs inversus was discovered three times in 51,246 hospital admissions. The authors discuss the diagnosis and complications of the disorder.

MACDONALD, Pittsburgh.

PTERYGIUM SYNDROME. E. ROSSI and A. CAFLISCH, Helvet. paediat. acta **6**:119 (April) 1951.

The authors review 177 cases from the literature, inclusive of 20 cases of their own, showing multiple malformations with pterygium formation. It is suggested that the classical picture should be referred to as the pterygium syndrome. Certain malformations recur regularly in most of the cases and allow a subclassification into five main groups, bilateral Ullrich syndrome, dystrophia brevicollis congenita, pterygonuchal infantilism, unilateral Ullrich syndrome and congenital pterygoarthromyodysplasia. The theories that have been advanced to explain the origin and pathogenesis of these conditions, especially those of Bonnevie, Bagg, Plagens, and Sturkie, are critically examined. Whether these theories apply to the human pathology requires confirmation. The authors state that the only deduction that can be made with certainty from a review of the literature and from their own observations is that the condition is hereditary.

FROM THE AUTHORS' SUMMARY.

STATISTICAL AND CLINICAL DATA REGARDING PREMATURE INFANTS ADMITTED TO THE CLINICA PER LE MALATTIE DEI BAMBINI DI TRIESTE IN THE YEARS 1940-1949. L. ROCCO and G. VIANELLO, Lattante **22**:26 (Jan.) 1951.

During the war years, there was a marked increase in the number of premature infants under 2,000 gm. admitted to the Trieste clinic; the premature death rate reached a maximum of 75% in 1944. In 1949, the rate had fallen to 31%, and to as low as 15% in infants whose birth weights were between 2,000 and 2,500 gm.

HIGGINS, Boston.

CONGENITAL HYPERTROPHY AND THE KLIPPEL-TRÉNAUNAY-PARKES-WEBER SYNDROME. L. PARENZAN and A. ZANINI, Minerva pediat. **3**:475 (Sept.) 1951.

The Klippel-Trénaunay-Parkes-Weber syndrome, also called hemangiectasia hypertrophicans, includes three congenital abnormalities, hypertrophy of a part of the body, cutaneous nevus, and varicose veins. The cases of three children, aged 1 month, 13 months and 24 months, with hemihypertrophy of the external ear and of the upper and lower extremities are reported. Only one of the three children had a cutaneous nevus, and none had varicose veins.

Abnormal vascular development is not necessarily accompanied by hypertrophy, but hypertrophy may be secondary to abnormal vascular development. Hypertrophy, with or without vascular changes, probably dates back to the early stages of embryonic development, when a varied number of cells received an added growth stimulus.

HIGGINS, Boston.

KLIPPEL-TRENAUNAY SYNDROME. HERMAN HEVIA, JORGE ROSSELOT, and RODOLFO BURDACH, Rev. chilena pediat. **23**:78 (Feb.) 1952.

A case of an 18-month-old infant with flat angiomas, varices, and distal hypertrophy of the extremities, with the Klippel-Trenaunay syndrome, is reported.

FROM THE AUTHORS' SUMMARY.

RIGHT ILIAC AGENESIS WITH LUMBOGLUTEAL EVENTRATION. P. DESMOULIN, Acta paediat. belg. **4**:59, 1950.

A case of absence of the right abdominal wall with eventration, and with malformations of the anogenital region and of the right foot is described. The x-ray revealed only nine ribs on the right side, malformation of the lower spinal column, absence of the right iliac bone, and underdevelopment of the bones of the right leg

GLASER, Jerusalem, Israel.

Newborn

SEQUENCES IN THE DEVELOPMENT OF CIRRHOSIS OF THE LIVER IN CASES OF ERYTHROBLASTOSIS FETALIS. JOHN M. CRAIG, Arch. Path. **49**:665 (June) 1950.

A study of the development of cirrhosis of the liver in erythroblastosis is presented. Of 141 infants examined at autopsy 16 were found to exhibit severe liver damage. Three groups could be defined, one (10 cases) showing midzonal parenchymal necrosis, the second (4 cases) showing necrosis and fibrosis, and a third (2 cases) showing cirrhosis. The incidence of the histologic changes seemed independent of the parity of the mother, the severity of the disease, the postnatal survival of the infant, and the related pathological conditions. The author discusses possible etiological factors in the production of cirrhosis. Before birth, as a consequence of the nature of fetal blood flow the liver receives undiluted a portion of any maternal antibodies that may have traversed the maternal placental barrier. At the time of delivery the passage of larger molecules and complete antibodies may take place more easily owing to the high intrauterine pressure during contraction. Postnatal continuation of hepatic damage is less easily explained. The author suggests that perhaps the liver has too great a burden with an increased metabolic demand occasioned by the presence of large numbers of erythropoietic elements and an anemic blood with poor carrying power for oxygen. The type of regeneration seen, tending to keep fibrosis more evenly and regularly distributed without compression, may be an expression of greater regenerative powers of the infantile kidney.

HAW CHAN, San Francisco.

THE ROLE OF BRONCHOSCOPY IN RESUSCITATION OF ASPHYXIA OF THE NEWBORN. H. L. BELL, Eye, Ear, Nose & Throat Month. **31**:601 (Nov.) 1952.

Bell makes a plea for early bronchoscopic examination and aspiration in cases of asphyxia of the newborn. Bronchoscopy should be advocated more universally for infants not responding to conservative therapy and for those beginning to show signs of exhaustion. The trial period of conservative treatment should not be prolonged at the risk of jeopardizing the viability of the cerebral cell structure. Bronchoscopy of the newborn should not be used as a last resort. Passage of the infant bronchoscope is not difficult, and in the hands of a skilled bronchoscopist it is relatively atraumatic.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

CONGENITAL INTRINSIC OBSTRUCTION OF THE STOMACH AND DUODENUM IN THE NEWBORN. CLIFFORD D. BENSON and JOHN J. COURY JR., Harper Hosp. Bull. **10**:1 (Jan.-Feb.) 1952.

In the newborn infant, a prepyloric diaphragm was successfully treated as described; it was the second reported in the literature. Ten patients with congenital intrinsic obstructions of the duodenum were operated upon, with seven survivals. Of the group of 11 patients, 7 were premature; two of the deaths occurred in premature infants weighing less than 3 lb. (1,360 gm.) at the time of surgical intervention. With earlier diagnosis and surgical treatment, the prognosis of the infant with congenital intrinsic gastric and duodenal atresia is more favorable than formerly, even though the infant is premature.

FROM THE AUTHORS' SUMMARY.

EXPERIENCES WITH AN ELECTIVE ROOMING-IN PROGRAM. MIRIAN MELLON PENNOYER, J. Pediat. **38**:213 (Feb.) 1951.

Pennoyer has successfully instituted a rooming-in program in an obstetrical department, without architectural changes in the hospital. She has utilized existing room arrangements and with the help of the regular nursing staff, and the mothers who are ambulant on the second or third day, has been able to satisfy most of the requirements for this plan. Mothers, nurses, and physicians, in her hospital, approve the plan.

MACDONALD, Pittsburgh.

ICTERUS PRECOX. I. HALBRECHT, J. Pediat. **39**:185 (Aug.) 1951.

Halbrecht calls mild hemolytic disease of the newborn "icterus precox." He suspects that it may sometimes be mistaken for physiologic icterus. Almost all his 90 cases were caused by maternal autoimmunization through the antigen A, B of the children. Two were cases of Rh incompatibility. Prognosis is usually good.

MACDONALD, Pittsburgh.

FORMULA ROOMS FOR NEWBORN INFANTS IN LYING-IN HOSPITALS. HELEN M. WALLACE, HAROLD ABRAMSON, and MARGARET A. LOSTT, J. Pediat. **39**:337 (Sept.) 1951.

Terminal sterilization of formulas, previously prepared with "clean" technique, is effective. Two methods of sterilization are available: (1) high and (2) low pressure methods. By the high pressure method moist heat is applied to the formula unit at 110 C. for 10 minutes under a pressure of about 7 lb. in a mechanically sealed container. By the low pressure method hot water and flowing steam are applied at 100 C. for 25 minutes in a closed water-vapor bath sterilizer.

MACDONALD, Pittsburgh.

PERFORATION OF THE STOMACH IN THE NEWBORN INFANT. HUSTON G. KELLOGG and SOL M. ABELSON, J. Pediat. **39**:357 (Sept.) 1951.

One cannot help but wonder at this precocious newborn infant who had his ulcer early. It ruptured and he was successfully operated on at 4 days of age.

MACDONALD, Pittsburgh.

CONGENITAL OBSTRUCTION OF THE ALIMENTARY CANAL IN THE NEWBORN. DAVID P. ANDERSON and ROBERT R. WRIGHT, Minnesota Med. **34**:1159 (Dec.) 1951.

Congenital obstruction of the alimentary canal is commoner than previous reports would indicate. It has previously been stated that atresia of the gastrointestinal tract occurs in approximately 1 in every 1,500 births. The authors reviewed 4,374 live births and found four cases of complete obstruction of the alimentary canal. A plea was made for more accurate diagnosis in the neonatal period, since surgical treatment of this problem is satisfactory when performed within 48 to 72 hours of life.

STOESSER, Minneapolis.

MODIFICATION OF TECHNIC OF TREATING ERYTHROBLASTOSIS FETALIS BY EXCHANGE TRANSFUSION. A. S. WIENER and I. B. WEXLER, Pediatrics **8**:117 (July) 1951.

A modification of the technic of exchange transfusion is presented, in which packed red blood cells are used instead of whole citrated blood. The advantages of using packed cells are that the duration of the procedure is reduced and that most of the citrate and adult plasma which are administered when whole blood is used are eliminated. At the same time, the need for calcium to counteract the tetanogenic effect of the citrate is also avoided.

A formula for calculating the percentage exchange when packed red blood cells are used for the infusion is presented. This formula takes into account the baby's blood volume, the hematocrit value of the baby's blood, the hematocrit value of the packed cells used for the infusion, as well as the volume of blood exchanged. From a table constructed with the aid of the formula, it is evident that the more anemic the baby is at the start of the procedure, the greater is the efficiency of the exchange, so that in this respect the more severely affected infants are the ones that are most benefited by the procedure. The usual quantity of packed cells used is 120 to 150 cc.

The mortality rates in three series of cases are compared. For those erythroblastotic infants for whom 500 cc. of whole blood was used for exchange transfusion the mortality rate was $23.7 \pm 4.6\%$; in those cases in which 1,000 cc. of whole blood was used the mortality rate was $14.6 \pm 3.4\%$, while with the use of packed red cells the mortality rate was $10.0 \pm 4.5\%$. The difference in mortality rates is not statistically significant, because of the small size of the series.

FROM THE AUTHORS' SUMMARY.

INFLUENCE OF DIET ON THE OCCURRENCE OF HYPERPHOSPHATEMIA AND HYPOCALCEMIA IN THE NEWBORN INFANT. ISAAC F. GITTLEMAN and J. B. PINCUS, Pediatrics **8**:788 (Dec.) 1951.

Studies on the effect of diets on the serum calcium and phosphorus levels in newborn infants were made. Human milk was found to be the most effective in maintaining a normal calcium and phosphorus level. Evaporated milk was found to be least satisfactory because it tends to

produce the largest number of instances of hyperphosphatemia and hypocalcemia. The desirability of adding vitamin D to the diets of infants in the neonatal period is questionable. In the infants studied the hyperphosphatemia and hypocalcemia were more marked than in those who did not receive this supplement.

FROM THE AUTHORS' SUMMARY.

GANGRENE OF THE FOREARM IN THE NEWBORN. R. J. K. BROWN and S. R. N. SMITH, Arch. Dis. Childhood **26**:574 (Dec.) 1951.

A case of gangrene of the left forearm in a newborn infant is described. In spite of amputation on the second day, fatal toxemia developed.

At necropsy, thrombosis was found in the aorta obstructing the mouth of the left subclavian artery. The blood stream in the descending aorta beyond the obstruction came from the right ventricle via the pulmonary artery and a widely patent ductus arteriosus, thereby simulating the altered circulation seen in the infantile type of coarctation of the aorta. The thrombus was thought to have originated by embolism from antemortem thrombus in the left auricular appendage.

The possibility of local pressure as an immediate cause of the gangrene is considered. Forty-six cases of gangrene in the newborn have been traced in the literature, some of which have been briefly discussed.

KELLY, Milwaukee.

AUREOMYCIN IN INFECTIONS OF THE NEWBORN. L. RIBADEAU-DUMAS, DEBRAY J. HÉRAUX, and VERLIAC, Presse méd. **58**:921 (Aug. 26) 1950.

Infections of the newborn are most often due to contamination from the maternal genitalia during delivery. One of the most constant signs of infection is sudden loss of weight.

The authors report the treatment of 13 infants with aureomycin. Results were much better than those obtained by the use of sulfonamides, penicillin, or streptomycin.

DAFFINEE, Melrose, Mass.

ERYTHROBLASTOSIS DUE TO MATERNAL ISOIMMUNIZATION TO HEMOAGGLUTINOGEN B. R. SEIGNEURIN, J. ROGET, J. GROULADE, and F. VIALLAT, Presse méd. **58**:939 (Sept. 2) 1950.

In a newborn infant jaundice developed soon after birth, and laboratory examination of the blood confirmed the clinical diagnosis of erythroblastosis. Baby, father, and mother were all Rh-positive, but the mother was of group O, while the infant and father were of group B. Anti-B-agglutins were present in the mother's serum, and also in her milk, in equal amounts.

Three transfusions were given to the baby, with an artificial mixture of blood composed of O cells suspended in an A B plasma. Results were excellent.

It is interesting to note that the transfusions were given into the sagittal sinus of the skull.

DAFFINEE, Melrose, Mass.

TRANSITORY GRANULOCYTOPENIA IN THE NEWBORN. H. LEHNDORFF, Helvet. paediat. acta **6**:173 (June) 1951.

In two newborn siblings severe granulocytopenia was observed. Onset was sudden on the third day of life, with disappearance of mature neutrophiles from the peripheral blood, the number of white cells approximately normal, and the number of monocytes high. The myelogram showed the typical picture of maturation arrest, a promyelocytic marrow. A dramatic reverse of the blood picture to normal within 24 hours was seen in case 2.

Transitory granulocytopenia in the newborn belongs to the group of the toxic-allergic neutropenias. It is a new phenomenon in the pathology of the newborn during the adaptation period; it is to be considered as a manifestation of allergy of the newborn.

GRULEE, Evanston, Ill.

STENOSIS OF DUODENUM FROM A MESENTERIC INFARCT IN A NEWBORN CHILD. S. QUADRI, Clin. pediat. **33**:329 (June) 1951.

A 40-day-old breast-fed baby had been vomiting bile-stained material projectilely after every feeding for 17 days. The appetite was good, but the urine and fecal excretions were scanty. He died eight days later. Postmortem examination revealed marked dilation of the first part of the duodenum up to a segment which was gangrenous owing to an enteromesenteric infarct.

HIGGINS, Boston.

HEMOLYTIC DISEASE OF THE NEWBORN FROM MATERNAL ISOIMMUNIZATION TO ANTIGEN A. G. SANSONE and C. ZUNIN, Lattante **22**:541 (Sept.) 1951.

A case of kernicterus in a 9-day-old child is reported with findings at autopsy. A subsequent pregnancy of the mother terminated in a miscarriage at the fifth month. The blood of both parents was Rh-positive; the father was of group A, and the mother of group O. There was a high anti-A level of antibodies (1:16,000) in the mother's serum one month after each pregnancy had terminated.

HIGGINS, Boston.

ETIOPATHOGENETIC FACTORS IN TETANY OF THE NEWBORN. E. SCHWARTZ-TIENE, Minerva pediat. **4**:1 (Jan. 15) 1952.

Tetany of the newborn may be traced to an abnormal calcium and phosphorus metabolism in utero. While vitamin D is of value in certain types of tetany, it only increases the symptoms if hypoparathyroidism is responsible. By reason of its higher calcium and phosphorus content, cow's milk seems preferable to mother's milk in tetany of the newborn.

HIGGINS, Boston.

EXCHANGE TRANSFUSION IN ICTERUS GRAVIS NEONATORUM. H. KOLBL and I. JUDTMANN, Wien. klin. Wchnschr. **63**:493 (July 6) 1951.

Total serum or plasma proteins were determined by Kjeldahl's method, while the protein fractions were determined electrophoretically. The total protein was diminished compared with that of normal newborn infants in eight cases of icterus gravis, with some diminution of the albumin fraction and some increase in the globulin fraction. In two cases the analyses were carried out after transfusion of each 50 cc. up to 450 cc. in one and after transfusion of each 100 cc. up to 400 cc. in the other. The most striking effect was an increase in fibrinogen. The donor blood was rather low in total protein and albumin, because the interval between bleeding of the Rh-negative donors was insufficient. In the first instance the total protein dropped at first to the concentration of the donor's blood. In the second instance the total protein also dropped somewhat at first but remained somewhat higher than that of the donor's blood. The blood of both infants gave a positive reaction to a blocking test which became negative after transfusion of 150 cc. The danger of an acute protein deficiency when washed erythrocytes are used for exchange transfusion is emphasized.

AMBERG, Rochester, Minn.

Acute Contagious Diseases

MENINGOCOCCIC MENINGITIS. ALEXANDER T. ROSS, A. M. A. Arch. Neurol. & Psychiat. **67**:89 (Jan.) 1952.

The incidence of residue following treatment with serum, sulfonamides, and combined sulfonamide-penicillin was studied. Fifty-one patients were given physical and neurological examinations, having recovered from the disease 1½ to 20 years previously. Thirty-two received electroencephalographic and psychometric studies as well.

No statistically significant difference was found in the incidence of defects following treatment by the various methods. However, physical defects were three times as common in those given serum or sulfonamides as in those given penicillin and sulfonamides. In the latter group defects were discovered only by psychometric evaluation. Apparently the addition of penicillin reduces the likelihood of the more severe complications.

McGUIGAN, Evanston, Ill.

EVALUATION OF THE CUIRASS RESPIRATOR IN ACUTE POLIOMYELITIS WITH RESPIRATORY INSUFFICIENCY. FRED PLUM, and DANIEL S. LUKAS, Am. J. M. Sc. **221**:417 (April) 1951.

The effects of a cuirass respirator have been evaluated on 10 patients with respiratory insufficiency due to acute poliomyelitis. Two patients were studied during their acute illness, five patients were studied during convalescence while they still needed artificial respiration, and three patients were examined at autopsy.

Blood acidosis, due to failure of carbon dioxide elimination from the lungs, was a manifestation of respiratory insufficiency in two acutely ill patients, and occurred in the absence of anoxemia.

Respiratory acidosis was not prevented or corrected in these two acutely ill patients by artificial respiration with a cuirass respirator, but was at least partially corrected by tank respirators.

Tank respirators produced from 34 to 100% greater tidal volumes at equivalent pressures than did a cuirass respirator on five convalescent patients with paralyzed respiratory musculatures. Anterior pulmonary emphysema was seen at postmortem examination in the three patients who died after treatment in the cuirass respirator.

Only when the advantages offered by the cuirass respirator are compelling, and when the amount of ventilation produced can be determined to be physiologically sufficient, does it seem desirable to use this device in its present stage of development.

HENSKE, Omaha.

STREPTOMYCIN IN THE TREATMENT OF PERTUSSIS. G. ARGEMI FONTANET, Arch. pediat. **1**:185 (Sept.) 1950.

The author, who has had no experience with aureomycin and hyperimmune serum, states that he has had excellent results with dihydrostreptomycin in the treatment of pertussis.

Of the 38 patients treated, 18 were under 1 year of age, and the others were under 5 years of age. The treatment was begun in the early convulsive stage; patients were rapidly relieved of symptoms. In two cases only was there lack of beneficial effects. There were no complications in any of the patients treated.

The dose was 40 mg. per kilogram of body weight per 24 hours. This was given by injection not oftener than every 8 to 12 hours.

Except for mild sedatives and vitamin C, no other medication was used.

ALLEN, San Francisco.

PATHOLOGICAL EMBRYOLOGY DUE TO RUBELLA. J. A. ALEMANY SITJA, Arch. pediat. **2**:1 (July) 1951.

This is a review of the congenital defects which may occur if the mother has German measles in the first trimester of pregnancy. The incidence in Australia appears highest; there is less reported in England and the United States, and still less on the European continent. The author feels that perhaps in Europe statistics have not been so carefully observed. There is also another factor—few epidemics of this disease occur in continental Europe especially among adults.

Perhaps other virus diseases should be carefully investigated for the possibility of similar findings.

The prophylaxis is discussed.

ALLEN, San Francisco.

POLIOMYELITIS—NEWER ETIOLOGICAL ASPECTS. J. G. VALL BANERES, Arch. pediat. **2**:9 (July) 1951.

The author considers the many different poliomyelitis-like viruses and classifies them according to whether they are neurotropic or myotropic. The histological findings are compared. The spontaneous type and possibilities for animal inoculation are classified under (1) true human poliomyelitis, (2) pseudopoliomyelitis in human beings, and (3) the disease in animals.

The coxsackie virus is included in pseudopoliomyelitis.

The various strains confer specific immunity after attack, but do not seem to confer immunity against similar strains. Only the cases of severe disease with paralysis seem to confer lifetime immunity, as the antibody titers in the serum of convalescents falls with time.

Specific and nonspecific therapeutic measures are discussed. Gamma globulin seems the best specific; it is better given at intervals in small dosage rather than in one large injection. Large doses of convalescent serum are next best. Whole blood may also have to be used in large amounts in the form of a transfusion to be of any value.

Many investigators have proposed the use of vitamin B, which is only of supportive value. The patient's diet should be rich in this vitamin. Its use in beriberi is specific, but the muscle weakness in poliomyelitis is not to be compared with that in this condition.

Corticotropin, aureomycin, and phenosulfazol were of no value, and the author believes corticotropin may actually be harmful.

At present vaccination is efficacious experimentally, but dangerous clinically, until further research is done.

ALLEN, San Francisco.

PERTUSSIS: CLINICAL COMPARISON OF THE NEWER ANTIBIOTICS. CRAIG E. BOOHER, JAMES FARRELL, and EDWARD J. WEST, J. Pediat. **38**:411 (April) 1951.

Aureomycin, chloramphenicol, and oxytetracycline were of almost equal value in the treatment of uncomplicated pertussis. The whoop stage was reduced about 60% by these drugs and, with the exception of aureomycin, the duration of fever was shortened. The suggested dose for the three drugs is 50 mg. per kilogram per 24 hours. Despite the favorable results reported here, no dramatic cures were effected. The specific drug for pertussis has not yet appeared.

MACDONALD, Pittsburgh.

TONSILLECTOMY AND POLIOMYELITIS: II. FREQUENCY OF BULBAR PARALYSIS, 1944-1949. MORRIS SIEGEL, MORRIS GREENBERG, and CATHERINE MAGEE, J. Pediat. **38**:548 (April) 1951.

Since 1910, when a possible relationship between bulbar poliomyelitis and tonsillectomy was first reported, medical opinion on this subject has been divided. The pediatricians support the theory, while the throat surgeons oppose it. Here, Drs. Siegel, Greenberg, and Magee did add fuel to the pediatric fire. They studied 194 cases of bulbar poliomyelitis occurring within one year after tonsillectomy. The number of cases is admittedly small, but they found a significantly higher incidence of bulbar paralysis in the group studied one month after operation. They also found an increase in the mortality rate in those cases seen within two months after operation. The percentage of cases was somewhat higher in the spring and fall than in the summer, and it would seem that bulbar paralysis after tonsillectomy is more frequent in nonepidemic than in epidemic years. The winter months are the safest for tonsillectomy, at least from the poliomyelitis point of view. In a five-year period, no post-tonsillectomy bulbar poliomyelitis was seen in New York during the winter months.

MACDONALD, Pittsburgh.

THERAPY FOR SPEECH DEFICIENCIES RESULTING FROM ACUTE BULBAR POLIOMYELITIS INFECTION. ELMER E. BAKER JR. and MARTIN A. SOKOLOFF, J. Speech & Hearing Disorders **16**:337 (Dec.) 1951.

Nineteen patients returning to the Department of Physical Medicine and Rehabilitation of Bellevue Hospital for periodic follow-up examinations subsequent to acute bulbar poliomyelitis showed a characteristic speech aberration consisting essentially of a flaccid paralysis of the velar musculature. Therapy undertaken with these cases was satisfactory in 12 patients; 4 attained a marked degree of improvement, while 8 showed degrees of improvement varying from marked to slight. The techniques used were blowing exercises, panting and yawning exercises, and massage of the velum. It was felt that in the cases not progressing there were certain emotional patterns which interfered with therapy.

PALMER, Wichita, Kan.

TRACHEOTOMY IN BULBAR POLIOMYELITIS. OREL FRIEDMAN and JOSEPH G. GILBERT, Laryngoscope **62**:1112 (Oct.) 1952.

Tracheotomy in bulbar poliomyelitis is done primarily to prevent anoxia and carbon dioxide accumulation due to secretional obstruction of the air passages. It is this anoxia that does more harm to the central nervous system than the virus of the disease.

Indications for tracheotomy are given, together with the advantage gained thereby. Six cases are reported.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

UPPER-RESPIRATORY INFECTION AS A FACTOR INFLUENCING SUSCEPTIBILITY TO POLIOMYELITIS. THEODORE H. INGALLS and W. LLOYD ALCOCK, New England J. Med. **245**:197 (Aug. 9) 1951.

In 1936, over a two-week period, 22 cases of poliomyelitis occurred among 190 boys in a Massachusetts school. The age group represented was from 12 to 19 years. The authors describe the clinical pattern of the cases and state that the distribution and character of this isolated outburst of poliomyelitis suggest a relationship between the upper respiratory infections which occurred prior to the onset of the illness and the clinical manifestations of poliomyelitis.

WHEELOCK, Denver.

POLIOMYELITIS OCCURRING AFTER ANTIGEN INJECTIONS. GAYLORD W. ANDERSON and AUDREY E. SKAAR, Pediatrics **7**:741 (June) 1951.

In view of the reports in the English literature suggesting a relationship between the location of paralysis in poliomyelitis and the site of recently antecedent antigen injections, epidemiologic histories gathered during the 1946 Minnesota outbreak were carefully reviewed. Among the children under 8 years of age, 85 patients were found who were known to have had antigen injections during the preceding six months; of these, 33 had had their injections during the preceding month. Arm paralyses were commoner among the first-month group than in those immunized two to six months earlier, or among those immunized before 1946 or among those never immunized. Similarly the cases were severer and showed a high degree of involvement of the extremity into which the antigen had been injected. Contrary to the British and Australian experience, which tended to incriminate pertussis vaccine, there was no apparent relationship to any particular antigen. No evidence was found to suggest that this effect of antigen in altering the reaction to poliomyelitis virus is a frequent occurrence or that it persists for more than one month. Since immunization is, in almost all cases, an elective procedure, it would seem expedient to postpone it during an outbreak of poliomyelitis. There is no reason, however, for discontinuing immunization, as this effect is purely temporary.

FROM THE AUTHORS' SUMMARY.

SIMULTANEOUS HERPES ZOSTER AND CHICKENPOX. S. D. AUSTIN, WILLIAM H. BRANDON, and ROBERT R. MCGEE, South. M. J. **45**:76 (Jan.) 1952.

Two adult cases of concurrent herpes zoster and chickenpox are presented. No photographs are included.

LOGAN, Rochester, Minn.

STUDIES ON POLIOMYELITIS IN ONTARIO WITH FURTHER OBSERVATIONS ON THE RECOVERY OF COXSACKIE VIRUSES FROM CASES OF CLINICAL POLIOMYELITIS. NELLES SILVERTHORNE and others, Canad. M. A. J. **65**:536 (Dec.) 1951.

Studies of 22 children admitted with a diagnosis of poliomyelitis are presented. Eleven children with clinical nonparalytic poliomyelitis were found to be excreting only Coxsackie virus. Ten children with paralytic poliomyelitis were found to harbor poliomyelitis virus, but three of these also had Coxsackie virus. One additional child with ascending paralysis of unknown etiology also had poliomyelitis virus. The authors suggest that many cases of clinical poliomyelitis, mainly of the nonparalytic variety, were in fact Coxsackie virus infections.

MCGUIGAN, Evanston, Ill.

CHLOROMYCETIN IN THE TREATMENT OF MUMPS. GRANVILLE DICKERSON and E. M. WORDEN, Canad. M. A. J. **66**:17 (Jan.) 1952.

Chloramphenicol failed to show any effect either in uncomplicated or complicated mumps.

McGUIGAN, Evanston, Ill.

CEREBRAL POLIOMYELITIS IN EARLY INFANCY. V. SMALLPIECE and C. OUNSTED, J. Neurol., Neurosurg. & Psychiat. **15**:13 (Feb.) 1952.

The first six months of life are generally considered to be a period of high immunity to poliomyelitis. This paper describes a small outbreak of poliomyelitis in a nursing home involving three infants, all probably infected from a common source, in whom the disease was followed by severe cerebral symptoms.

The patients were infants, 7, 3, and 2 weeks of age. All had multiple lower motor neuron paralyses. One died in convulsion during the convalescent phase of the disease. One child survived for two years nine months but was idiotic, with multiple paralyses and fits. He died after a seizure, and necropsy revealed the typical lesions of poliomyelitis in the spinal cord. One child was alive at the time of the report, but was also an epileptic idiot, with upper and lower motor neuron paralyses and athetosis.

The authors suggest that the midwife, who attended the three children described in this paper, was the vector. She was entirely healthy throughout the episode.

The clinical features and epidemiological aspects of cerebral poliomyelitis in early infancy are described and discussed.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PUNCTATE BASOPHILIA IN PERTUSSIS. F. DRAPER, Clin. Rep. Adelaide Child. Hosp. **2**:59 (May) 1951.

Basophilic stippling occurring in pertussis is described, occurring in 10 of 26 cases. The stippling seemed to be more noticeable as spasms of coughing increased.

McGUIGAN, Evanston, Ill.

TREATMENT OF DIPHTHERIA. AMALANADA DAS, J. INDIAN M. A. **20**:282 (May) 1951.

The author outlines the treatment he recommends for diphtheria. In general it follows accepted procedures in this country.

McGUIGAN, Evanston, Ill.

VALUE OF CHLOROMYCETIN IN THE TREATMENT OF WHOOPING COUGH. A. KHALIL and ZABERA H. ABDIN, J. Roy. Egyptian M. A. **34**:735, 1951.

The authors treated children in varying stages of pertussis with chloramphenicol. They conclude that in the early stages the drug is valuable, averting the disease or transforming it into a rather insignificant ailment. Later in the disease it appears to be of some value in many of the cases, but not in all.

McGUIGAN, Evanston, Ill.

ELECTROCARDIOGRAM IN POLIOMYELITIS. W. FRISCHKNECKT and H. ZELLWEGER, Helvet. paediat. acta **5**:448 (Nov.) 1950.

Twenty-one of 52 patients with poliomyelitis (40.3%) showed changes in their electrocardiograms; 18 of them (34.6%) had pathological T-waves and in 3 cases there were disturbances in the auricular conduction.

Before the 15th day of the disease, pathological T-waves in cases of poliomyelitis often are spontaneously reversible (10 cases); partly, they also can be normalized by a sympathicolytic agent within 45 minutes after subcutaneous injection (case 1). This shows the probability of an extracardial vegetative disregulation of the heart in poliomyelitis.

In poliomyelitis, those changes in the electrocardiogram that last longer than two or three weeks suggest myocarditis. The authors found only four of such cases, in three of which disturbances in the auricular conduction lasted four months (Cases 1 and 3, together with one case of the Wolff-Parkinson-White syndrome).

The question is discussed whether those long-lasting changes in the electrocardiogram are caused by poliomyelitis insult of the autonomic nervous system, or whether there exists a direct influence of the virus on the myocardium.

FROM THE AUTHORS' SUMMARY.

EXTRAPYRAMIDAL MANIFESTATIONS IN THE CHILD WITH VARICELLA. D. CORDA, Ann. ital. pediat. **4**:503 (Dec.) 1951.

The author in 1933 described three cases of nervous complications in children affected by varicella. He now reports a rather rare manifestation of extrapyramidal type and with sudden onset, with symptoms suggesting pseudoencephalitis lethargica (hypersomnia, hypertonia, transient tremors, rigidity of plastic type, impossibility of taking food and deglutition).

The nervous and general system soon had a remission, first rapid and then slower, to result (after about five months) in a very slight hypertonia.

Discussing the etiopathogenesis of the localization, the author thinks (as in the previous cases) that the varicella virus in a predisposed individual, perhaps from a familial nervous weakness, might have caused congestive alterations (inflammatory, infiltrative and strongly hemorrhagic) of the globus pallidus and partly perhaps of the black substance of the body of Luys and the hypothalamus.

FROM THE AUTHOR'S SUMMARY.

EXANTHEMATOUS RASH DURING INCUBATION PERIOD OF MEASLES. G. TONIOLO, Clin. pediat. **33**:43 (Jan.) 1951.

Two instances are cited of a temporary exanthematous rash appearing on the 8th and 10th days of the incubation period of measles, and two days before the recognition of Koplik spots.

HIGGINS, Boston.

ACTION OF AUREOMYCIN IN THE VIRUS OF VACCINIA. A. DEGLI ESPOSTI, Clin. pediat. **33**:461 (Aug.) 1951.

A 10-month-old child with eczema vaccinatum, appearing 18 days after a positive Jennerian vaccination, was treated with aureomycin as outlined by Perry and Martineau (*J. A. M. A.* **141**:657, 1949), but without the spectacular results noted by those authors.

Children receiving 0.5 to 1.0 gm. of aureomycin daily after vaccination had less fever and less local reaction than did controls.

After vaccine serum had been mixed with aureomycin in amounts up to 75 γ per cubic centimeter and had been kept at a temperature of 37 C. for eight hours, the virus was still alive as evidenced by successful vaccination takes. Similarly 500 γ aureomycin per cubic centimeter of vaccine serum and stored at 1 C. for 15 days left the virus still active. However, the virus was no longer active after 100 γ aureomycin per cubic centimeter of vaccine serum was kept at 37 C. for eight hours, or 500 γ per cubic centimeter at 1 C. for 30 days.

HIGGINS, Boston.

ACTUAL INJURY FROM JENNERIAN VACCINATION. D. GOTTI, Clin. pediat. **33**:617 (Oct.) 1951.

Over a ten year period (1940 to 1950) at the Pediatric Clinic of the University of Bologna, there were three cases of meningoencephalitis (2 being fatal) and one case of polyneuritis following vaccination for smallpox. There were no cases of generalized vaccinia among those vaccinated prophylactically, but there were four cases of accidental vaccinia, two involving the eyelid, and two generalized, one of them in a child with eczema. Penicillin and streptomycin were of little therapeutic value in the generalized cases, but aureomycin did seem to have some beneficial effect in effecting a rapid cure.

HIGGINS, Boston.

EPIDEMIOLOGICAL CHARACTERISTICS OF DIPHTHERIA AND ITS RELATION TO PROPHYLACTIC VACCINATION. D. GOTTI, Clin. pediat. **33**:715 (Nov.) 1951.

Statistics are recorded as to diphtheritic infection over the years 1931 to 1949, as observed at the Ospedale Gozzadini, where 75% of the patients with that disease in Bologna are hospitalized. Of the 3,266 cases, 269 (8.2%) terminated fatally. The highest mortality was in the cases of

laryngeal disease. The incidence was highest in the months of January and May. Little change was found in the yearly incidence between 1931 and 1946; the largest number was in 1945, the last war year, when there was an epidemic with 407 cases. Beginning in 1947, there has been a definite lessening in the number of cases. This diminution is especially marked in children of school age, between 6 and 13 years. It is very necessary to continue to urge prophylaxis among adults and smaller children, the groups in which prophylactic vaccination is not now required.

HIGGINS, Boston.

ACUTE POLIOMYELITIS IN THE PROVINCE OF PAVIA BETWEEN 1939 AND 1949. M. CLERICI, Lattante **22**:207 (April) 1951.

Two hundred eighteen cases of infantile paralysis in children were reported in the Province of Pavia during the decade 1939 to 1949. The bigger epidemics were in 1941 (38 cases) and 1949 (48 cases). The mortality rate was 8.7%. The disease seems to be endemic in a plain along the road between Pavia and Mortara. There is no indication that the disease has spread along waterways.

HIGGINS, Boston.

PERTUSSIS: A CLINICAL AND THERAPEUTIC REVIEW. G. TACCONE, Lattante **22**:693 (Dec.) 1951.

This lecture covers the clinical and therapeutic aspects of pertussis, especial attention being directed to the more recent studies reported in the literature.

HIGGINS, Boston.

SEVERE WHOOPING COUGH AND STREPTOMYCIN. ANTONIO PEREZ-FERNANDEZ, Acta pediat. españ. **8**:829 (July) 1950.

Dr. Fernandez describes the case of a child of 21 months who had been very healthy, well nourished, and with negative personal and family history. She was treated first with hyperimmune serum. She became gravely ill with bronchopneumonia.

Since both pneumococci organisms and Hemophilus pertussis were isolated from throat secretions, penicillin and sulfadiazine were tried but without improvement; vitamin C was used throughout and nikethamide and adrenal extract had to be resorted to on occasion to prevent circulatory collapse.

When penicillin failed, streptomycin was given with an initial dose of 0.25 gm. and continued with 0.15 gm. every three hours until a total of 3 gm. had been given. By the time 2 gm. had been given, the dyspnea, pallor, and fever disappeared. The breathing lost its stertorous quality. By the time the 3 gm. had been taken the child was free of symptoms and had only a slight cough.

The author believes streptomycin should be tried in severe cases of pertussis but should (because of its scarcity and possible toxicity) be used only in severe cases.

ALLEN, Santa Fe, N. Mex.

PERSONAL OBSERVATIONS CONCERNING ACUTE ANTERIOR POLIOMYELITIS IN THE LAST THREE YEARS. CALOMO DE LA VILLA, Acta pediat. españ. **8**:1017 (Sept.) 1950.

Dr. de la Villa discusses some of the characteristics of poliomyelitis epidemics encountered in the last three years and concludes that, although there are many unknown factors in the disease, it is certain that the virus is always traceable to a fecal contamination of water or food. The virus may be so attenuated as to give the abortive form of poliomyelitis; epidemics occur when the contamination is heavier or a new or more virulent strain is added to the "excretory reservoir."

There is no doubt that there are several strains of similar virus and that there are in laboratory animals certain signs of specificity. Some species may be immune to certain strains and be infected by other strains of virus.

The disease may affect children in a thoroughly hygienic environment because the children cannot always be kept from ingesting contaminated material.

Dr. de la Villa has found definite vitamin A and D deficiency in children who contracted poliomyelitis, regardless of economic status.

Epidemics occur in a given area and may not recur for some years in an epidemic form. Having the disease no doubt confers an immunity but without the production of demonstrable antibodies. Between epidemics the persons who have had the disease have the virus present in their alimentary tract and by elimination add to the excretory reservoir always present.

If the patient is highly susceptible the nervous system invasion leads to paralysis, and no specific therapy is known. Antibiotics, sulfonamides, neostigmine, curare, etc., are wasted in these cases. Although the author says that diet is also of no avail, he uses diets high in fatty acids, amino acids, and vitamins, especially A and D.

After the acute stage, physical therapy and orthopedic surgery should be immediately available.

The author believes there is not an unusual incidence of psychosis in poliomyelitis, and that psychoses which do develop are not of unusual severity, in view of the amount of parental anxiety present in this disease.

ALLEN, Santa Fe, N. Mex.

PHYSIOPATHOLOGY OF IMMUNITY IN THE INFANT. FELIX SANCHO MARTINEZ, Acta pediat. españ. 9:1299 (Nov.) 1951.

In a full and scholarly manner, Dr. Martinez discusses various factors in the immunity of the child at various ages to various diseases.

Three factors condition the immunity of the newborn infant, (1) the constant evolution to physiological maturity, (2) the contact with environmental forces, bacteria, viruses, etc., and (3) the type of defenses inherited from germ plasm, as well as antibodies, toxins, and organisms which have penetrated the placenta. These latter may be very evanescent or may be serious enough to give rise to congenital defects. The severity depends on the age of maturity at which the mother had the illness as well as its ability to penetrate the placenta.

Constitutional factors include both the inherited genotype and the phenotype.

The use of antepartum vaccinations and immunizations against various diseases shows wide range in the amount of antibody which is able to cross from the maternal to the fetal circulation. For example, the protection against diphtheria and tetanus is stronger and more permanent than that against pertussis.

Immune bodies appear not in the milk but in the colostrum. There may be local immunity at different age levels in the vernix caseosa, cornea, intestines, lungs, etc.

Plasma proteins and electrophoresis in relation to immune bodies are discussed. Allergy and the mechanisms in its development, with a diagram first elaborated by Teysche, are included. The relation between immunity and allergy is not completely understood, but many factors are known. In children with a labile nervous system, the vegetative nervous system plays a large role in the cutaneous reactions. There are differences in the immediate and delayed response in the child and the adult. The role of histamine and of the endothelial system is very important in children.

In a previous study the author showed that infants up to 7 months showed negative tuberculin response although their mothers had active tuberculosis during their gestation.

The antibody titer for a number of organisms was found to be quite different at approximately the same time in the maternal blood, the cord blood, and the infant blood.

The author made a study of the age at which various organisms appeared in the feces and pharynx and correlated the degree of immunity the infants developed to these organisms. The organisms were of the Escherichia group in the feces and the Streptococcus, the Staphylococcus and the Neisseria group in the pharynx. The cultures were taken hourly for 24 hours, then monthly for 30 months. Adult level of immunity to these specific organisms was approached by the end of 36 months. On necropsy on this age group, nervous system lesions were found; not lesions of the intestines. The author believes that the immaturity of the intestinal tissue as contrasted with the nervous tissue accounted for this finding.

The effect of too long hospitalization on the psychic and physical immunity is shown to be a vicious circle, since infection brings on psychological retardation and depression which, in turn, diminish the vital impulses and organic defenses, and this makes the child more susceptible to another infection.

Climatic factors are also discussed.

The author has made a study, which is still being carried on, in which he attempts to relate the development of certain diatheses to the type of footprints of the babies and the mothers' fingerprints.

In subjects with the anuclear type of whorl called A, lymphatic and exudative diathesis is more likely to predominate, while those with type B, a semicircular type of whorl, seemed to be more immune to tuberculosis and intestinal infections.

The place of antibiotics and new drugs in future immune reactions is discussed.

In conclusion, the child progresses toward a more perfect type of immunity, inherited and acquired, but interrupted by imbalance of humoral, vegetative, and hormonal factors which may be transformed into allergic and other manifestations. ALLEN, San Francisco.

CONSIDERATIONS REGARDING ONE THOUSAND CASES OF PERTUSSIS TREATED WITH STREPTOMYCIN. FLORENCIO BOZAN, ENRIQUE SUJOY, and SARA GEILER, Acta pediat. españ. **9**:1373 (Nov.) 1951.

The results are reported of a study of 1,000 cases of whooping cough in the Children's Hospital in Buenos Aires in the service of infectious diseases in that city.

In children under one year, the mortality fell from 41.1% to 19.29% after the use of streptomycin. In children of 5 years and over, there were no deaths after the use of the antibiotic, although there were 4% before the use of streptomycin in this age group. These are total figures.

The deaths from complications were also reduced greatly except in the cases in which encephalitis was the complication of the whooping cough. ALLEN, San Francisco.

TREATMENT OF WHOOPING COUGH IN THE NEWBORN WITH CHLORAMPHENICOL. MANUEL NAVARRO GARCIA, Acta pediat. españ. **9**:1376 (Nov.) 1951.

The author reviews the literature on the treatment of whooping cough in the newborn and reports three cases of infants under one month with severe whooping cough who recovered with treatment with chloramphenicol. Diagnosis was made by epidemiological as well as by positive laboratory findings. Older children in the family had pertussis and, because the mother thought the newborn children were immune, these newborn infants were not isolated and contracted the disease at 23, 18, and 22 days, respectively.

The fever, coughing bouts, etc., improved rapidly after the third day of medication. The author discusses the deleterious effects reported in the literature, but there were no side-effects in the cases reported. The chloramphenicol was given by mouth in suitable vehicles or by rectum. The initial dosage was 250 mg. by rectum mixed with a mucilaginous vehicle, followed by 60 mg. mixed with mother's milk, honey, or fruit juices to which sugar was added.

After the attacks of convulsive coughing stopped, there was some coughing of a nonconvulsive type, but all symptoms disappeared by the time the children were 39, 40, and 43 days old, respectively. Graphs representing the symptoms included the weight gains in each infant. The chloramphenicol was given for five days. The antibiotic was started after three days of clinical evidence of pertussis.

The author says that three cases are not conclusive, but more of such should be reported, if possible, as the literature does not include many cases of infants under one month of age.

ALLEN, San Francisco.

IMMUNIZATION HAZARDS. F. ESCARDO, Arch. argent. pediat. **36**:186 (Sept.) 1951.

Escardo reviews the various reactions (central nervous system, renal, gastrointestinal, and those due to contamination) to various immunizing agents. PANOS, Galveston, Texas.

ISOLATED ACCOMMODATION PARALYSIS FOLLOWING MUMPS. BELTZ and BOUCHEL, Rev. oto-neuro-opht. **24**:159 (April) 1952.

Paralysis of accommodation after mumps is a rare complication. Previous cases have been reported, but the authors had never seen this complication, although they report having seen

complained of visual difficulties and was unable to read the newspaper. Orchitis appeared at the same time. On his admission to the hospital, 18 days later, the orchitis and parotitis had cleared up. The external appearance of the eyes, the ocular movements, and the fundi were all normal. Impaired vision was correctible by the use of lenses. There was no evidence of diabetes mellitus or diphtheria; the accommodation paralysis was not due to asthenia. The function of accommodation gradually returned to normal. For four days after admission there was mild meningeal irritation. No mention of lumbar puncture was made. The authors report that the pupils reacted well to light and in convergence. They note that the ocular complication in this case occurred during the first week, while the parotid glands were still enlarged, and lasted one month. N. SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

TIME AT WHICH VACCINIA VIRUS INJECTED INTRAVENOUSLY CAN BE DEMONSTRATED IN THE BLOOD. WILHELM REINHART, Wien. klin. Wchnschr. **63**:925 (Dec. 7) 1951.

Suspensions of vaccine virus were injected intravenously in rabbits and guinea pigs. By means of staining reactions of the buffy coat, or whole citrated blood, and in some instances by means of inoculation of the leucocytes in the guinea pig cornea, it could be shown that the virus was no longer demonstrable two hours after injection, but it reappeared in the blood on the second day and could be found regularly to the fifth day. AMBERG, Rochester, Minn.

INFECTIOUS DISEASES OF CHILDHOOD AND THEIR TREATMENT. KARL KUNDRATITZ, Wien. klin. Wchnschr. **63**:951 (Dec. 21) 1952.

A short table, concerning five recent years, lists in Austria approximately 60,000 cases of diphtheria with 4.6% mortality; about 56,000 cases of scarlet fever with about 0.3% mortality; about 30,000 cases of pertussis with about 4% mortality, and about 6,000 cases of poliomyelitis with about 9.3% mortality. The malignant toxic form of diphtheria is discussed. Special attention is accorded to the investigations of O'Meara, who demonstrated in every diphtheria toxin two components, the prevalence of one of which determines the high toxicity. The author found in such cases high sugar content of the cerebrospinal fluid. Occasionally, though, a low content was found. With regard to treatment the early administration of large doses of antitoxin is stressed. In cases of severe periglandular edema of the neck local injections of antitoxins are recommended. An antitoxin of great avidity for the toxin, obtained by the use of toxin containing both components in appropriate amounts, promises much better results than the usual antitoxin. At any rate, a small number of patients with severely toxic diphtheria so treated recovered. Quite a number of other therapeutic measures are discussed, directed at the various manifestations, with special emphasis on myocardial involvement. Penicillin applied locally and intramuscularly, particularly in cases of respiratory tract involvement, is recommended, as well as streptomycin. The necessity of protective active immunization is stressed. With regard to scarlet fever the treatment recommended in severe and toxic cases is transfusions, reconvalescent serum and antiscarlet fever serum, besides penicillin, which is the most important therapeutic agent. The administration of pertussis vaccine is credited not only with protective, but also with therapeutic effect. Streptomycin has been used by the author with success. Hyperimmune serum, or its gamma globulin, is also accredited as useful. The effect of various forms of therapy in cases of poliomyelitis has been decidedly less than in other infectious diseases.

AMBERG, Rochester, Minn.

NEW RESULTS OF STUDIES OF THE ETIOLOGY AND PATHOGENESIS OF INFECTIOUS DISEASES. R. BIELING, MARBURG, Wien. klin. Wchnschr. **64**:1 (Jan. 4) 1952.

The paper deals with the virus of grippe and poliomyelitis and its relatives. It is stressed that a first attack in children may produce in the infected person a minimal illness. Afterward the person appears in good health, but the virus remains still present. When, during this period, an unspecific stimulus elicits another illness—primary disease—acute typical poliomyelitis may supervene. A natural infection, like an experimental one in animals, leads in some of the infected individuals to the disease. In others an insufficient dosage, or individual resistance,

produces a latent infection. If the infected individual is not subjected to other unspecific injuries before the latent virus is excreted, it remains well, and becomes immune to exogenous reinfection. When a case of poliomyelitis occurs, the importance of guarding others against injury is stressed.

AMBERG, Rochester, Minn.

NEW ASPECTS OF POLIOMYELITIS. S. VAN CREVELD, Maandschr. kindergeneesk. **29**:479 (Jan.) 1952.

Poliomyelitis has aspects of special interest even outside periods of epidemics. One has always to keep in mind that in poliomyelitis there occur many more nonparalytic cases than paralytic ones. In addition to the already known factors favoring the occurrence of clinical symptoms, we now have to deal with a new problem, that of the possible influence of prophylactic vaccination on the occurrence of poliomyelitis. In this connnection, the recommendation to omit all vaccinations in children during an epidemic of poliomyelitis, especially in those older than 6 months, deserves special attention.

It has been established experimentally that cortisone favors the growth of poliomyelitis virus. It is still questionable how far the use of cortisone in man has an influence on the frequency of poliomyelitis, and especially on the frequency of paralytic cases.

The researches of Enders and others on tissue culture of the poliomyelitis virus are of very great importance for the study of the whole problem of poliomyelitis. The fact that propagation of the virus in tissue culture may be followed by changes in its pathogenicity for mice, and that vaccination with such a weakened virus may give protection in certain circumstances against a subsequent inoculation with virulent virus, may be of value for the prophylaxis of human poliomyelitis in the future.

The researches of recent years have brought into the foreground the question of a relationship between the poliomyelitis virus and the Coxsackie virus and the diseases caused by both (poliomyelitis and Bornholm disease, respectively).

Special attention is drawn to the diseases caused experimentally by the Coxsackie virus and to the possible significance of these diseases in human pathology. In this connection a case is discussed of encephalohepatomyocarditis observed in a baby by the author.

The recent work of Casal on a complement-fixation test for the diagnosis of poliomyelitis is discussed, as well as the recent researches in the United States on the number and spread of the different types of poliomyelitis viruses in man, and their clinical significance.

Finally, it is stressed that in many countries the mean age of persons with poliomyelitis has increased of late.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

VALUE OF AUREOMYCIN IN PREVENTION OF CROSS INFECTION IN THE HOSPITAL FOR SICK CHILDREN. C. E. SNELLING and ROBERT JOHNSON, Canad. M. A. J. **66**:6 (Jan.) 1952.

Control of widespread cross infection in the Toronto Children's Hospital was accomplished by use of aureomycin. The infection was a gastrointestinal one which responded to treatment with aureomycin. Because of the success in controlling cross infections aureomycin was given to all premature babies prophylactically. No gastroenteritis developed, and it was felt that the babies looked better and gained weight a little faster than others not so treated. Premature infants were given 50 mg. daily.

McGUIGAN, Evanston, Ill.

ANTITYPHOID VACCINATION BY RECTUM. P. PINNA, Ann. ital. pediat. **4**:514 (Dec.) 1951.

The author reports the results obtained through vaccinal therapy given with rectoclysis in drops to 109 children with typhoid. Its action was ready and quick in 66.6% of cases with an amelioration of general conditions and fall of temperature within a few days; it was less quick in 17.7% and slight in 15.7%.

These results are comparable to those found in children treated with intravenous therapy, and avoids the phenomena of shock; the results are absolutely higher than those in children treated with intramuscular therapy.

No reaction, either local or general, was seen, the only obstacle being diarrhea or rectal conditions which may prevent absorption. Therefore, the author thinks that when possible, this therapy is to be preferred to all others, including therapy with chloramphenicol, which does not show particular advantages.

A union of the two therapies is not to be excluded, as it shortens the course of the disease and also gives the possibility of an earlier intervention.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF ECHINOCOCCUS CYST OF THE LUNG IN THE CHILD. PASQUALE ROMUALDI, Arch. ital. pediat. puericolt. **15**:45, 1951.

Fifteen cases of Echinococcus cysts of the lung in children are described. In four cases the cysts were multiple; there were 20 cysts in total. All the cases were observed from June 1, 1947, until the time of writing, in the surgical section of the Hospital "Bambino Gesu" in Rome. All the cysts were monolocular, two were suppurated, and one was accompanied with a pulmonary abscess.

All the patients were treated by single operation without marsupialization and with closing of the thorax (Posadas); the anesthetic was administered endotracheally. There were 19 interventions. The advantages of the method consist especially in the shortness of the postoperative course.

Methods for treatment of Echinococcus cysts of the lung are briefly and critically described. A case is reported in which, because of the anatomicopathologic peculiarities, the cyst was not removed, but it was only punctured, and sterilization was followed by recovery. Some brief remarks are made on the treatment of suppurated Echinococcus cysts of the lung.

FROM THE AUTHOR'S SUMMARY.

TYPHOID IN CASES OF TUBERCULOUS MENINGITIS UNDER STREPTOMYCIN THERAPY. P. NICOLAI, Clin. pediat. **33**:484 (Aug.) 1951.

Three children with tuberculous meningitis were responding well to treatment with streptomycin, when each contracted typhoid. Chloramphenicol was given. Two of the children recovered, but the third died from encephalitic symptoms and adhesions in the spinal canal, due to the tuberculous infection. It is gratifying to observe that a recovery may be possible in what has always been regarded as a universally fatal complication of tuberculous meningitis.

HIGGINS, Boston.

BLOOD AND MARROW CHANGES IN RHEUMATIC INFECTIONS OF CHILDHOOD. M. VERROTTI, Clin. pediat. **33**:525 (Sept.) 1951.

Smears from the blood and the bone marrow of 14 children with rheumatic fever revealed (1) leucocytosis with neutrophilia, hyperplasia of the medullary granuloblasts, and often eosinophilia, (2) hypochromic anemia with signs of an increased rate of maturation of the erythroblastic cells in the marrow, and (3) monocytosis with often very atypical-appearing cells. The leucocytosis is ascribed to the infectious and the eosinophilia to the allergic nature of the disease. The anemia is believed to be induced by infectious noxa, and the monocytosis to changes in the blood chemistry.

HIGGINS, Boston.

BRUCELLOSIS IN CHILDHOOD. DR. GUSTAVO ROSS B., Rev. chilena pediat. **11**:525 (Nov.) 1951.

Three cases of brucellosis in children treated with a combination of streptomycin and a sulfonamide drug with good results are reported. After observation periods of one to two years no relapses were noted.

FROM THE AUTHOR'S SUMMARY.

TYPHOID AND CHLORAMPHENICOL. FIDEL URRUTIA, Rev. chilena pediat. **22**:564 (Dec.) 1951.

To 45 children, 3 to 12 years old, with typhoid, 250 mg. chloramphenicol was administered every six hours without a larger initial dose. No deaths were observed.

FROM THE AUTHOR'S SUMMARY.

AMEBIASIS IN THE CHILD. R. ORTEGA and H. SUAREZ, Rev. chilena pediat. **23**:50 (Feb.) 1952.

The authors have verified that amebic dysentery occurs very frequently among their hospital patients and that in childhood it affects infants almost exclusively (51 of 54 cases). As it has been shown that amebic infection is very widespread among the population of any age, they suppose that the older child has a relative tolerance to it, or that the infection more often has clinical manifestations other than the dysenteric one.

Most of their patients are malnourished because of dietetic deficiencies or amebiasis or both. Intercurrent or concomitant infections are thus very frequent, as well as admittance to the hospital due to grave dehydration with or without the toxic syndrome. The dysenteric type of stool (blood, mucus, pus) presents itself at some moment during the disease, in the past history, on admittance to the hospital, or afterward. The presence of this kind of stool with a history of periods of diarrhea and periods of well-being makes a diagnosis of amebiasis very probable. Confirmation is obtained by means of parasitological examinations of stools and proctoscopy.

Of 51 infants, eight died, amebiasis being the direct cause in three and a factor which greatly contributed to death in the other 5.

FROM THE AUTHORS' SUMMARY.

RECTOSCOPY IN AMEBIASIS IN CHILDREN. CARLOD TREUER, Rev. chilena pediat. **23**:58 (Feb.) 1952.

Rectosigmoidoscopy proved to be an excellent complementary method of diagnosis in children suffering from amebic dysentery. Under treatment the first evidence of cure is the disappearance of parasites from the stools and the last the normalization of stools and specially of the mucosa of the rectosigmoid as seen with the rectoscope. Thus endoscopy is to a certain extent the best way to pronounce the disease cured or still active.

FROM THE AUTHOR'S SUMMARY.

CHLORAMPHENICOL TREATMENT OF TYPHOID AND PARATYPHOID IN CHILDREN. ERICH HAGENDORFF, Arch. Kinderh. **143**:27, 1951.

Clinical analysis is made of four observations. Treatment with chloramphenicol results in rapid improvement that has never been attained before. The therapeutic application does not involve any technical difficulties, since the capsules may be taken in honey or other food.

The dosage of 50 to 100 mg. per kilogram is sufficient. It is imperative to continue the treatment long enough to prevent relapses. The high initial dose should be abandoned, since it favors the development of circulatory complications. Recurrences respond to repeated treatment. The drug does not have any effect upon carriers.

GOTTSTEIN, Chicago.

INFECTION WITH LAMBLIA IN CHILDHOOD. H. WALENZ, Kinderärztl. Praxis **17**:387 (Nov.-Dec.) 1949.

Three cases of Giardia lamblia infection are described in children between 8 and 10 years of age. The symptoms may vary from acute gastroenteritis to chronic enterocolitis. Symptoms of liver or gall-bladder disease were described in one of the three cases. Diagnosis was established by microscopic demonstration of G. lamblia in the duodenal juice after instillation of 25% magnesium sulfate. The treatment consisted of three to five days of quinacrine in doses of either 0.1 gm. three times daily or 0.06 gm. five times daily.

Since the presence of G. lamblia is not proof of its pathogenicity, only disappearance of symptoms following specific therapy and demonstration of the organism can be considered as diagnostic.

GLASER, Jerusalem.

ROENTGEN EXAMINATION IN ASCARIDIASIS. NORBERT ZYLKA, Med. Klin. **47**:1227 (Nov. 23) 1951.

Under certain conditions x-ray examination can make Ascaris infestation evident; for instance, when in the presence of the male worm, no eggs are demonstrable in fecal material. Aside from filling defects, the barium sulfate contrast medium can be deposited on the skin of the worms, but it also may be ingested, as shown by experiments in which the worms were placed in an isotonic saline solution in which some barium sulfate was suspended.

AMBERG, Rochester, Minn.

TYPHOID TREATED WITH CHLORAMPHENICOL. E. GLORIEUX, Acta paediat. belg. **4**:1, 1950.

Clinical observations and review of the literature lead to the conclusions that chloramphenicol is the drug of choice in the treatment of typhoid; its action seems bacteriostatic rather than bacteriocidal, which explains its ineffectiveness in the treatment of carriers. The development of agglutinating antibodies does not seem influenced by treatment, and it is thus to be assumed that natural immunity develops in treated persons as well as in untreated. No resistant strains and no toxicity attributable to chloramphenicol have been observed. Large oral doses at frequent intervals are recommended as most effective. In case of inability to swallow, the rectal route can be tried.

GLASER, Jerusalem, Israel.

CORTICOTROPIN AND CORTISONE TREATMENT OF ACUTE RHEUMATIC FEVER. C. G. BERGSTRAND, B. HELLSTROM, and B. JONSSON, Acta paediat. **40**:502 (Nov.) 1951.

Three patients of rheumatic fever were treated with corticotropin and four with cortisone. All cases showed signs of cardiac involvement. During treatment the erythrocyte sedimentation rate rapidly fell to normal. Heart murmurs and pericardial friction sounds decreased or disappeared in all but one case, in which the treatment was started late in the course of the illness. Electrocardiographic changes present in six cases disappeared. In one case symptoms reappeared one month after treatment.

In one patient treated with corticotropin electrocardiographic changes, apparently caused by potassium deficit, occurred. No other side reactions were observed.

The adequate dosage of corticotropin and cortisone in treatment of children with rheumatic fever is at present not definitely established. For treatment with corticotropin the decrease in the number of eosinophiles seems to be a valuable guide.

At the present stage it is impossible to decide whether treatment with corticotropin or cortisone can prevent damage to the heart. Observation of a larger number of patients for several years will be necessary before this important question can be answered.

FROM THE AUTHORS' SUMMARY.

THE CHOICE OF THERAPEUTIC MEANS IN INFECTIOUS CONDITIONS. J. E. MINKENHOF, Maandschr. Kindergeneesk. **20**:119 (May) 1952.

In infectious diseases, convalescent serum, hyperimmune serum, and γ-globulins have an excellent prophylactic action but no therapeutic value. Virus diseases and harmless transient disorders with a favorable prognosis should not be treated with chemotherapeutic agents and antibiotics. In nearly all infectious diseases cortisone and corticotropin are contraindicated. In these conditions, it is usually advisable to administer the cheapest chemotherapeutic agent or antibiotic, of which the activity was first recognized, for as short a period as possible and in the smallest possible quantities. In the event of untoward side-effects or resistance, a newer drug should be selected. Certain combinations of antibiotics are less effective than the substances separately. In the treatment of infectious diseases, the determination of the resistance of pathogenic agents has a qualitative and corrective but not a quantitative significance.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

TUBERCULIN NEGATIVE TUBERCULOSIS. WILLI MASCHER, Am. Rev. Tuberc. **63**:501 (May) 1951.

There are two basic observations on the question of the significance of the tuberculin reaction concerning which there seems to be unanimity of opinion, that persons not infected with tuberculosis cannot be rendered sensitive to tuberculosis by tuberculin even when it is given in large doses and, that a positive reaction signifies that the subject harbors a tuberculous focus brought about by infection with living or dead Mycobacterium tuberculosis. It is also recognized that the interpretation of the reaction implies nothing about the activity or clinical significance of the existing focus.

According to the author the reaction may be said to be positive only when there is an infiltrative area at least 5 by 5 mm. with the Pirquet reaction and at least 10 by 10 mm. with Mantoux technic, which persists at least 48 hours. The reaction may be considered negative when there is failure to react to intradermal injection of 1 mg. of 1:100 dilution.

While a positive reaction as described above always signifies the existence of tuberculous infection, under certain conditions a negative reaction may persist in subjects in whom tuberculous infection undoubtedly must have occurred. It is possible, by the application of increasing doses of tuberculin, gradually to desensitize a positive reactor. During the stage of incubation and during the existence of certain nontuberculous infectious diseases, reactions may temporarily remain negative. Such may be the case during miliary spread of the disease, in tuberculous meningitis, in certain cachectic conditions, and in old age. It has been the prevailing opinion that a person who has once been positive will retain this mode of action throughout life. It has been demonstrated recently, however, that in certain tuberculin-positive healthy persons, when followed over a period of years, the reaction will be found to have reverted from positive to negative.

In this communication Mascher calls attention to another group of patients of much greater clinical significance, patients with active tuberculosis and negative tuberculin reaction. To illustrate the findings in this group, the author recounts in detail the case histories in 11 cases of undoubted active tuberculosis in which the tuberculin skin test remained persistently negative. Included are eight cases in which repeated examinations demonstrated the presence of acid-fast organisms. In three cases, while the organisms could not be demonstrated, the history, x-ray findings, and course of the disease fully justified the diagnosis of active tuberculosis. The ages of these patients, with the exception of a 12-year-old girl, ranged from 30 to 59 years. All patients failed to react to the intracutaneous injection of 3 mg. of old tuberculin.

EUGENE SMITH, Ogden, Utah.

PROGNOSTIC VALUE OF THE EVANS BLUE TEST IN TUBERCULOUS MENINGITIS. R. RAMOS, M. DE LA IGLESIA, and W. APPENHEIMER, Arch. pediat. **2**:31 (July) 1951.

The authors present three cases of tuberculous meningitis treated with streptomycin. The prognosis was determined in these cases by the use of Evans blue injected in the spinal fluid. The technique is described and the clinical findings are given in graphs. In cases in which the curve of the Evans blue maintained a value between 13 and 25 colorimetric units the prognosis was best.

Initial total discoloration which continues in other readings from the spinal taps is a bad prognostic sign, showing an abnormal permeability of the blood-brain barrier, whereas continued high readings may mean a previously existing block. ALLEN, San Francisco.

HISTOPLASMOSIS. MILDRED CARIKER, Minnesota Med. **35**:213 (March) 1952.

Histoplasmosis occurs in infants. It occurs in a subclinical form and as such has residual lesions in the lungs which must be differentiated from tuberculosis. Methods of culture of the etiologic agent, Histoplasma capsulatum, are well known. A positive skin test for Histoplasma is beneficial in diagnosis of healed or subclinical histoplasmosis. STOESSER, Minneapolis.

FACTORS AFFECTING PROGNOSIS OF TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. LAURENCE FINBERG, Pediatrics **8**:768 (Dec.) 1951.

A series of 35 consecutive unselected cases of tuberculous meningitis treated with streptomycin is presented briefly. The over-all survival rate with a minimum observation period of six months is 37.2%. The longest survival observed is 49 months.

It is shown that for this group of cases of tuberculous meningitis the coexistence of roentgenographic evidence of miliary lesions in the lungs changed the prognosis for survival from 55% to 13%. It is also noted that applying this factor to the published data from other clinics seems to resolve in part some apparent discrepancies in results. It would therefore appear wise for future clinical reports to separate cases of tuberculous meningitis which have concomitant miliary lesions from those which do not. FROM THE AUTHOR'S SUMMARY.

SENSITIVITY STUDIES IN VITRO WITH HISTOPLASMA CAPSULATUM TO VARIOUS POTENTIAL THERAPEUTIC AGENTS: ARILD E. HANSEN and MARY LOUISE BEENE, Proc. Soc. Exper. Biol. & Med. **77**:365 (June) 1951.

A 6½-month-old white girl with fever, cough, and enlarged abdomen had been given a diagnosis of acute lymphatic leukemia. Bone marrow biopsy revealed the presence of intracellular yeast-like cells in the macrophages which led to the diagnosis of histoplasmosis. Cultures of the blood and bone marrow yielded Histoplasma capsulatum. The organism isolated from the bone marrow was maintained in the yeast phase by frequent transfer on blood agar slants. In vitro studies were made with various substances known to be harmful to certain protoplasmic structures. The test materials were γ-benzene hexachloride, Δ-benzene hexachloride, quinine bisulfate, quinacrine, emetine, 2,4-dichlorophenoxyacetate, aminosalicylic acid, urethan, and ethyl vanillate. Ethyl vanillate was the only agent that showed promise as a possible therapeutic agent.

ARILD E. HANSEN, Galveston, Texas.

STUDIES OF THE CEREBROSPINAL FLUID CIRCULATION IN TUBERCULOUS MENINGITIS IN CHILDREN: PART II. A REVIEW OF 100 PNEUMOENCEPHALOGRAMS. JOHN LORBER, Arch. Dis. Childhood **26**:43 (Feb.) 1951.

One hundred pneumoencephalograms were performed on 58 children suffering from tuberculous meningitis. With the possible exception of one case, no serious after-effects were noted. No relapse of the meningitis followed within two months of any examination.

In 18 children normal conditions existed 4 to 14 months after the treatment was begun.

Abnormalities were found in 36 children. In six of these a previous pneumonencephalogram had been normal. Three main abnormalities were detected. 1. One or more blocks other than spinal ones were found in 30 cases. In all these there was a block at the tentorial opening or in the basal cisterns. In two cases there was an additional block at the Sylvian aqueduct, and in three others in the foramina of the fourth ventricle. These blocks were usually present at or soon after the beginning of treatment. 2. In no case of tentorial or basal cisternal block was there subarachnoid air. This sign preceded the hydrocephalus in three cases. In only four children was any degree of hydrocephalus seen when subarachnoid air was present. Subarachnoid air must be distinguished from subdural air, which may occur in any encephalogram. 3. Hydrocephalus of varying degrees was found in 34 cases. Clinical recovery was almost complete in eight of these children. Repeated pneumoencephalograms in six of them showed an increase in the degree of the hydrocephalus in three, no change in two, and a decrease in one. In three hydrocephalic children cerebral cysts developed, in two cases spontaneously and in the other following a ventricular puncture. The etiology of the cysts is discussed.

A close correlation was found between encephalographic appearances and prognosis. After a minimum follow-up period of 11 months 16 of 18 children with normal encephalograms were alive and only 1 of the survivors was left with serious neurological sequelae. One of the deaths was not due to meningitis. Of 26 children with abnormal encephalograms only 8 were alive after the same period of observation. They all have neurological or mental residual lesions, and these are serious in five. Of nine persons with meningitis who had relapses, five had normal encephalograms and survived. The four others died.

KELLY, Milwaukee.

TUBERCULOUS PERICARDITIS. R. MCLAREN TODD, Arch. Dis. Childhood **26**:83 (Feb.) 1951.

Tuberculous pericarditis is still considered to be a rare disease in childhood, but the recognition at the operation of the tuberculous nature of a high proportion of cases of constrictive pericarditis suggests that the disease may occur more frequently than it is diagnosed.

Even when suspected the diagnosis is difficult to confirm either by guinea pig inoculation or by biopsy of the pericardium.

The primary and secondary types of tuberculous pericarditis are discussed, and the clinical details of a case of tuberculous pericarditis resulting from the rupture of a caseous gland adherent to the pericardium are described together with other cases in which the gland of the ductus arteriosus (Engel's gland) was responsible for the spread of tuberculosis to the peri-

cardium. The involvement of this gland may be merely fortuitous, but the anatomical situation of the gland, contiguous with the pericardium at its reflection, would readily facilitate pericardial involvement.

KELLY, Milwaukee.

TUBERCULOUS ISCHIO-RECTAL ABSCESS AND PRIMARY TUBERCULOUS COMPLEX IN A FIVE-MONTHS-OLD INFANT. B. GANS, Arch. Dis. Childhood **26**:85 (Feb.) 1951.

A case of a primary pulmonary tuberculous complex, complicated by an ischiorectal abscess, is reported in a 5-month-old child. The tuberculous nature of the perianal lesion was proved by histopathological methods.

KELLY, Milwaukee.

NEUROSURGICAL METHODS IN THE TREATMENT OF TUBERCULOUS MENINGITIS. SIR HUGH CAIRNS, Arch. Dis. Childhood **26**:366 (Oct.) 1951.

Frontal burr holes for tapping the lateral ventricles have proved to be necessary in about one-third of the author's cases of tuberculous meningitis treated with streptomycin. Apart from this minor operation, neurosurgical procedures are not called for in most cases. However, there is the occasional case in which a major operation to deal with some unusual cause of raised intracranial pressure is essential to save life. During streptomycin treatment, each case should be frequently reassessed by thorough neurological examination and study of the cerebrospinal fluid charts, and ventriculography or cerebral angiography should be undertaken if the headaches are unusually severe, if there are signs of disturbed function of a cerebral hemisphere, or if the case is taking an unusual course during treatment.

KELLY, Milwaukee.

DELAY IN DIAGNOSIS OF TUBERCULOUS MENINGITIS AND ITS RELATION TO RESULTS OF TREATMENT. JOHN LORBER, Proc. Roy. Soc. Med. **44**:1 (Jan.) 1951.

Excellent results can now be obtained in the treatment of tuberculous meningitis with streptomycin if treatment begins in the early stages of the disease. On investigating the history of 87 children suffering from tuberculous meningitis, it was found that an average delay of over 14 days occurred from the time the symptoms developed until adequate treatment was begun.

As the average duration of this disease when untreated is approximately 21 days, the odds against successful treatment after the disease has been present for 14 days are very great. Mortality increases from 14% for immediately treated patients to 88% if treatment is begun after the 14th day.

Delays were found in three categories, (1) an average delay of over three days between the onset of symptoms and the physician's first visit, (2) a delay averaging over eight days between the physician's first call and the child's admission to the hospital, and (3) a delay of much shorter duration between the child's admission to the hospital and the beginning of adequate treatment.

It is strongly recommended that all children who are found to have positive tuberculin tests or any history of contact should be very carefully examined, always with tuberculosis in mind. The immediate diagnostic procedures in any suspected meningitis should be a lumbar puncture, x-ray of the chest, and examination of the retina for choroidal tubercles. If these diagnostic procedures are immediately carried out, there should rarely be a delay beyond a few hours in beginning adequate treatment.

Five tables are presented.

HEARD, Monterey, Calif.

PRENATAL SYPHILIS IN ONE OF TWINS. R. V. RAJAM and P. N. RANGIAH, J. Indian M. A. **21**:186 (Feb) 1952.

Congenital syphilis in twins is discussed, with reference to the literature and consideration of etiological factors. Various possibilities as to the reason for one twin's escaping are discussed. The author stresses the fact that the transmission of prenatal syphilis is capricious and unpredictable.

MCGUIGAN, Evanston, Ill.

CONGENITAL SYPHILIS. I. KESSELL, South African M. J. **26**:1 (Jan. 5) 1952.

The author presents five cases of congenital syphilis, with x-ray illustrations. Electrocardiographic changes are demonstrated in one case. The series is presented to illustrate x-ray changes in long bones in early infancy.

McGUIGAN, Evanston, Ill.

CONGENITAL TOXOPLASMOSIS. JEROME RABKIN, and S. N. JAVETT, South African M. J. **26**:41 (Jan. 19) 1952.

A case of congenital toxoplasmosis is presented, showing four of the major criteria for diagnosis: microcephaly and mental retardation, focal choroiditis, calcification in the brain, and positive serological tests in mother and child. Clinical, pathological, and roentgenological features of congenital toxoplasmosis are discussed, and the literature is briefly reviewed.

McGUIGAN, Evanston, Ill.

STREPTOMYCIN TREATMENT IN SEVERE CASES OF PRIMARY TUBERCULOSIS DURING EARLY CHILDHOOD. J. CHAPTAL, D. BRUNEL, and R. JEAN, Pédiatrie **38**:671, 1949.

Twenty-six children with primary tuberculosis were treated with streptomycin (0.75 to 1.5 gm. daily) for as long as five to six months. The length of treatment was determined not only by the clinical improvement but by definite signs of roentgenologic changes. Whereas in the lighter forms treatment for two to three months was sufficient, certain types, especially adenotuberculosis, showed particular resistance and needed five to six months of treatment. In spite of the long treatment no case of deafness occurred.

GLASER, Jerusalem.

DIAGNOSTIC VALUE OF THE SEROLOGIC TEST OF S. ARLOING AND P. COURMONT IN PRIMARY TUBERCULOSIS IN CHILDHOOD. M. BERNHEIM, Pédiatrie **38**:685, 1949.

The value of the agglutination reaction is discussed for the diagnosis of cases in which the tuberculin skin test remains negative for a long period and in the evaluation of the need and efficacy of BCG immunization or reimmunization. The test is found very valuable.

GLASER, Jerusalem.

SPINAL FLUID CHLORIDE DETERMINATIONS AS GUIDES TO DIAGNOSIS AND TREATMENT OF TUBERCULOUS MENINGITIS. J. TAPIE, J. MONNIER, A. DELAUDE, and GONTIER, Presse méd. **58**:809 (July 15) 1950.

The values of spinal-fluid chlorides are remarkably constant. A progressive decrease in the values of the chlorides is a diagnostic sign of tuberculous meningitis. If the use of streptomycin is effective in a case of this malady, the spinal-fluid chloride value will rise.

When the chloride content of the spinal fluid is normal, intrathecal administration of streptomycin may be stopped, although intramuscular treatment must be continued for a long while.

DAFFINEE, Melrose, Mass.

"HEAD" ZONES AND TUBERCULOSIS OF THE LUNGS. P. MIESCHER, Schweiz. med. Wchnschr. **82**:121 (Feb. 9) 1952.

Ninety-three patients, aged 10 to 20 years, were examined for Head zones. In 44 patients a disturbance of the skin sensibility was found, mainly in cases with scar formation. Twenty children with fresh primary complexes, demonstrated by x-ray, did not present a Head zone.

AMBERG, Rochester, Minn.

INTRAPARENCHYMAL TREATMENT WITH STREPTOMYCIN OF PULMONARY TUBERCULOSIS OF CHILDREN. S. STEFANINI, Clin. pediat. **33**:265 (May) 1951.

Thirty-three children with tuberculous pulmonary infiltration received injections of 50 to 200 mg. streptomycin into the diseased lung area daily or every two days. Two series of 10 to 15 injections were given with an intervening rest period of seven days. The therapeutic results

were cure of 7 children, improvement of 13 and lack of change in 13. The intraparenchymal streptomycin treatment appeared to be rapid and effective. The streptomycin was dissolved in isotonic salt solution, 100 mg. in 2 cc. The safety of the procedure was first tested on animals. A lumbar puncture needle was used; caution must be used to be certain that a blood vessel or a bronchus is not entered before the drug is injected.

HIGGINS, Boston.

XANTHOPROTEIN REACTION AND INDICAN IN THE SERA OF CHILDREN WITH TUBERCULOSIS. G. CERNUSCHI, Clin. pediat. **33**:509 (Aug.) 1951.

Xanthoprotein from the sera of 24 children with active tuberculosis was found to be in slightly higher amounts than in normal children. Indican determinations in the sera of the same children were found to be within normal limits.

HIGGINS, Boston.

SUBCUTANEOUS GRANULOMATOID REACTIONS IN TWO INFANTS, VACCINATED WITH PETRAGNINI'S ANATUBERCULIN BY THE PETRAGNINI-SALVIOLI METHOD. M. MALOSSI, Clin. pediat. **33**:547 (Sept.) 1951.

Two infants were vaccinated with Petragnini's anatuberculin on the forearm during the first week of their lives. Some weeks later, when the usual resulting reaction had appeared, there was also nearby a large subcutaneous swelling which in each case was firm, but not red or warm to the touch. Biopsies indicated that the swellings were granulomatous reactions of the subcutaneous tissue. The reactions are believed to be of an allergic nature.

HIGGINS, Boston.

THERAPEUTIC RESULTS WITH PENICILLIN IN A CASE OF SYPHILITIC MENINGOENCEPHALITIS IN A BOY OF TWO YEARS. I. TRAINA, Lattante **22**:34 (Jan.) 1951.

In a boy of 2 years previously treated for congenital syphilis fever, irritability, drowsiness, and pareses developed; the spinal fluid was slightly cloudy, contained 1,070 cells, mostly lymphocytes, and showed positive Pandy and Wassermann reactions. Treatment was with penicillin, 25,000 units every three hours; on the first day there was a Herxheimer reaction; treatment was continued, however, for 18 days. At that time, the spinal fluid was clear with no cells, but the Pandy and Wassermann reactions were still positive.

HIGGINS, Boston.

RECURRENCES OF TUBERCULOUS MENINGITIS. E. COSSANDI, Lattante **22**:658 (Nov.) 1951.

Recurrences of tuberculous meningitis were observed in three cases once and in two cases twice after the spinal fluid had become normal and the child had been discharged as cured. In three instances, the recurrences were within one month, in one after three months, and in three after one year. Only one of the children died. Treatments were with streptomycin and *p*-aminosalicylic acid; the recurrence usually responded to treatment more rapidly than the original attack.

HIGGINS, Boston.

SOME CASES OF TUBERCULOUS MENINGITIS OCCURRING DURING STREPTOMYCIN THERAPY. B. CARLETTI and M. L. QUARTI, Minerva pediat. **3**:195 (April) 1951.

Eleven children, 4 under 2 years of age and 7 older, contracted tuberculous meningitis while under treatment with streptomycin for pulmonary or miliary tuberculosis. The streptomycin treatments were begun 20 to 90 days before the meningeal symptoms appeared. The dosage of streptomycin given up to that time was between 6 and 50 mg. The symptoms of meningitis in these children were milder than are usually observed in that disease; the pathology appeared to be localized. Tuberculosis bacilli were proved to be present in the spinal fluids by culture or animal inoculation. Each of the patients recovered after intrathecal streptomycin injections.

While intramuscular administration of streptomycin did not prevent the tuberculous meningitis, it did modify its severity. It is quite probable that the tuberculosis bacilli were localized in or near the meninges before the intramuscular treatment started. The suggestion is made that a dose of streptomycin be given prophylactically in cases of active tuberculosis in children.

HIGGINS, Boston.

TRYPTOPHAN REACTION IN TUBERCULOUS MENINGITIS IN CHILDREN. G. GRANATA and L. PARENZAN, Minerva pediat. **3**:435 (Aug.) 1951.

A positive tryptophan reaction was obtained in the spinal fluid of 8 out of 15 cases of tuberculous meningitis, in 18 of 29 cases of tuberculous meningitis under streptomycin treatment, and in none of 41 cases with clear, but abnormal, spinal fluids (meningismus, poliomyelitis, encephalitis, hydrocephalus). While a positive reaction in a clear spinal fluid is a very probable diagnostic indication of tuberculous meningitis, it should not be taken as positive proof.

HIGGINS, Boston.

OSTEOPOROSIS IN THE COURSE OF THE STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINIGTIS. P. DURAND, Minerva pediat. **3**:538 (Oct.) 1951.

In about 50% of children with tuberculous meningitis and receiving streptomycin medication osteoporosis developed. These children were found to show a negative calcium balance between intake and output. The blood calcium in all but one of 24 cases studied was over 9.8 mg. per 100 cc. The blood phosphate was invariably low, averaging 3.0 mg. per 100 cc. No cases of tetany were observed.

Fourteen of 15 children with nonmeningeal tuberculosis receiving streptomycin for 2 to 10 months did not have osteoporosis. The blood calcium and phosphates in these patients averaged 9.6 mg. and 3.6 mg. per 100 cc.

The osteoporosis in the meningitis patients is believed to be due to a probably tuberculous pathological change in the diencephalon and pituitary tissues; this change would lead to functional reactions of other endocrine glands, especially the parathyroid and adrenal glands. Analogous conditions of pituitary cachexia and of adiposogenital dystrophy are reported in the literature in cases of tuberculous meningitis, in which streptomycin has prolonged life.

HIGGINS, Boston.

SIGNIFICANCE OF THE REACTION OF THE SPINAL FLUID IN TUBERCULOUS MENINGITIS DURING STREPTOMYCIN THERAPY. S. VIRDIS, Pediatria **59**:366 (May) 1951.

The colloidal benzoin test of Guillan, Laroche, and Lechelle on the spinal fluid is a very sensitive indicator of the therapeutic success of streptomycin treatment for tuberculous meningitis. Repeated negative tests indicate recovery, while even slight deviations following some negative tests are warning signs of an impending relapse.

HIGGINS, Boston.

LANGE'S COLLOIDAL GOLD REACTION IN THE CEREBROSPINAL FLUID OF TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN: SPINAL FLUID CLEARED. P. PERITI and C. CALANDI, Riv. clin. pediat. **49**:338 (May) 1951.

The authors discuss the clinical importance of Lange's reaction for recording changes in the cerebrospinal fluid (C.S.F.) during treatment of tuberculous meningitis with streptomycin, basing their observations on several hundred cases admitted to the Pediatric Clinic of Florence during the period of December 1946 to June 1949.

The colloidal gold reaction of Lange was found to be a suitable method to detect even the slightest changes, either qualitative or quantitative, of the proteins in the fluid. The colloidal reaction is not specific for the tuberculosis meningitis treated with streptomycin, as it is possible to observe various types of reaction in different cases in relation to the degree of involvement of the fluid, and even in the same patient on different levels of the central nervous system, corresponding to a different protein content.

There are two fundamental types of reaction when the cerebrospinal fluid reactions are studied from their earliest stages. In the first type, more frequent, the colloidal curve is "meningitic" before becoming gradually negative. The second type, less frequent, passes through a phase in which the curve is more or less "paralytic," and ends as the first type, becoming first meningitic and finally negative.

The first type is characteristic of those cases of tuberculous meningitis that finish rapidly and favorably, or those that proceed with moderate increase of the protein content to (50 to 80 mg.

per 100 cc.), while the second type is more characteristic of those cases in which recovery is slower and in which, during certain phases of the illness, there is a noticeable increase of the protein content (more than 150 mg. per 100 cc.). Every other course of Lange's reaction in the cerebrospinal fluid of tuberculous meningitis falls into one of these two fundamental types.

The Lange reaction places in evidence at the very begining alterations of the cerebrospinal fluid in grave cases of tuberculosis other than meningitis, especially if for some months the patient has been treated with streptomycin by intramuscular injection. At the same time, in the phase when the cerebrospinal fluid returns to normal, the Lange reaction is useful as a criterion of whether or not to interrupt the intrathecal therapy.

Since, when the intrathecal therapy is interrupted as soon as the cerebrospinal fluid becomes negative to the colloidal reaction, there is still a possibility of relapse, the negativity of this reaction cannot be considered an absolute guarantee of a lasting recovery. The authors hold that it is therefore necessary to continue the intrathecal therapy for some months after the cerebrospinal fluid has become normal according to their method.

The recovery of the cerebrospinal fluid progresses in time from the superior levels of the central nervous system toward the inferior levels during the therapy of tuberculous meningitis. The cerebrospinal fluid at the lumbar level is the last to present the return to negativity of the Lange reaction, sometimes many months elapsing with respect to the normalization of the sub-occipital spinal fluid. Therefore only when the cerebrospinal fluid at the lumbar level has become normal, can one speak of its normalization.

FROM THE AUTHORS' SUMMARY.

EXTINCTION VALUES IN THE PROGNOSIS AND TREATMENT OF TUBERCULOUS MENINGITIS. ALVARO MASI and MARCELLO GUISTI, Riv. clin. pediat. **49**:470 (July) 1951.

The authors have studied the behavior of streptomycin concentrations introduced intrathecally during the course of tuberculous meningitis at intervals of 8, 12, and 24 hours after introduction of the antibiotics. These concentrations, called "extinction values," are subject to variations peculiar to each patient and to each phase of the illness. Extension values afford, with the diffusion index, a very important source of exact knowledge of the inflammatory reaction of the spinal fluid situation in each patient and a very useful guide to rational therapy. They also are an important tool for prognosis, since they reveal the intensity and persistence of the local inflammatory process.

AUTHORS' SUMMARY.

EPITUBERCULOUS PROCESSES IN CHILDHOOD WITH SPECIAL REFERENCE TO THEIR PATHOGENESIS. V. BINDI and L. LENZINI, Riv. clin. pediat. **49**:631 (Sept.) 1951.

A report is given of what has already been written on the nature, on the symptomatology, and, more particularly, on the pathogenesis of epituberculous processes. It is followed by the illustration of 30 cases, chosen among 420 patients who were under observation for two years.

The authors think they can affirm that epituberculous processes are due to bronchial stenosis (primary trunks, lobar bronchial or zonal ramifications) and pulmonary atelectasis (total, lobar, plurizonal, or monozonal), and that they occur especially in infancy, as this age affords two favorable conditions for the development of the two above-mentioned diseases, the smallness and the compressibility of the bronchial tubes, on the one hand, and the strong reaction (of hyperplastic type) of the lymphatic system, on the other hand.

Hilus adenitis of the lungs is responsible for the occlusion and consequent atelectasis of the inferior pulmonary zone as a result of the increased volume of the nodes.

FROM THE AUTHORS' SUMMARY.

VIOMYCIN AND VIOMYCIN-STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS PRODUCED WITH STREPTOMYCN-RESISTANT GERMS. ALVARO MASI and PIERO MOGGI, Riv. clin. pediat. **49**:853 (Dec.) 1951.

The authors describe the favorable results obtained by treating with viomycin and a combination of viomycin and streptomycin guinea pigs infected with a strain of tuberculosis bacilli highly resistant to streptomycin.

The results were particularly evident in the animals treated with the combination of viomycin and streptomycin.

FROM THE AUTHORS' SUMMARY.

STREPTOMYCIN THERAPY IN MILIARY PULMONARY TUBERCULOSIS WITH EXPERIMENTAL TESTS ON RABBITS. SEVERINO PEDONE and ORESTE BRUNO BARTOLI, Riv. clin. pediat. **49**:871 (Dec.) 1951.

The authors, after referring to researches made by others, in the experimental and clinical fields, on the influence of streptomycin therapy on the evolution of pulmonary miliary tuberculosis, describe the results obtained by them in experimental research on pulmonary miliary tuberculosis in rabbits. With early streptomycin treatment it is possible to check the serious clinical and anatomicopathologic picture evident in the control animals, all of which died after a short time. It is possible for rabbits to be clinically cured with early streptomycin treatment; this did not happen when treatment was started in a later period. The influence of streptomycin on the anatomicohistological evolution of pulmonary tuberculous lesions has been studied; they were replaced by lesions of an exudative-necrotic type and subsequently replaced by lesions of a productive type, with tendency to fibrosis and incapsulation. On the whole streptomycin is able to check the rapidly encroaching and progressive course of experimental pulmonary miliary tuberculosis in rabbits, as has been observed in human beings.

FROM THE AUTHORS' SUMMARY.

OSTEOCYSTIC FIBROUS TUBERCULOSIS TREATED WITH STREPTOMYCIN. C. ALLIENDE, M. NEIRA, R. GALLEGOS, and E. ROSENBLUT, Rev. chilena pediat. **22**:549 (Dec.) 1951.

The authors report 7 cases of osteocystic tuberculosis, or Jüngling's disease, involving both long and short bones, as well as the facial bones. The patients were between 15 months and 11 years old. In most of the pulmonary primary complex was relatively unimportant, and the course of the bone lesion was prolonged and torpid. An excellent response to streptomycin was noted from the first injections, manifested by an osteosclerotic reaction followed by a complete bone restitution. Two patients who did not receive streptomycin had a protracted course over two years. A positive Kahn reaction was obtained in one patient and also in parents of three other patients. A probable effect of syphilis on the development of osteocystic tuberculosis is advanced by the authors.

FROM THE AUTHORS' SUMMARY.

ACUTE GLOMERULONEPHRITIS IN CHILDREN TREATED WITH ANTIHISTAMINICS. F. GONSALEZ LOPEZ, R. CAMPOS, and S. DE BONADONA BALBONTIN, Rev. chilena pediat. **23**:43 (Feb.) 1952.

Twenty children with acute glomerulonephritis were treated with antihistaminics (diphenhydramine) given by mouth. Twenty patients were used as controls. The two groups were placed under the same general conditions and patients were distributed alternately according to hospitalization, in either group. The following major syndromes were studied comparatively, cardiovascular, edematous, and urinary syndromes, renal function, as well as the number of days of hospitalization and the status at discharge. The authors concluded that acute glomerulonephritis in children is not influenced by the antihistaminic used.

FROM THE AUTHORS' SUMMARY.

MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN AT THE GENOA CHILDRENS' HOSPITAL G. DE TONI, Monatsschr. Kinderh. **99**:24 (Jan.) 1951.

Of 141 patients with tuberculous meningitis 70%, and of 72 with miliary tuberculosis 76.4%, recovered completely over a three-year period. There were daily intrathecal injections of streptomycin, 20 to 80 mg. depending on age, for two to three months; then the dose was decreased and, after four to six months, streptomycin was given every other day. This was continued at least one month after normal cerebrospinal fluid findings were noted. Daily intramuscular injections of 130 mg. of streptomycin per kilogram of body weight, administered in four to six divided doses with four to five days' rest after every month of treatment. Intramuscular injections of streptomycin were continued until cerebrospinal fluid findings had become normal. Additional intraventricular or suboccipital injection of streptomycin in half the intra-

thecal dose was given only when partial or complete block existed. It was found beneficial to include paraaminosalicylic acid in the dose of 0.3 to 0.4 gm. per kilogram per day by mouth. Addition of high doses of vitamins A and D was not thought to be beneficial.

HARTENSTEIN, Milwaukee.

BCG VACCINATION IN AUSTRIA. F. PUNTIGAM, Wien. klin. Wchnschr. **64**:77 (Feb. 1) 1952.

The paper gives a review of BCG vaccination in the various parts of Austria for the year from the first of July, 1950, to the end of June, 1951. All the pertinent data have been or will be published in more detail elsewhere.

AMBERG, Rochester, Minn.

ELECTROENCEPHALOGRAM IN TUBERCULOUS MENINGITIS. J. LESNY and A. J. HOUSTEK, Pediat. listy **4**:199, 1951.

Electroencephalograms were performed on 46 children with tuberculous meningitis treated with streptomycin; 14 children were aged 1 to 4 years, 28 from 4 to 10 years, and 4 were older than 10 years. The electroencephalograms were taken in the first month of the disease in 6 children, in the second to fourth month in 7 children, in the sixth to ninth month in 10, and later in the others. Normal curves were found in 19 children. Of the pathological changes a generalized abnormality without focal lesions was the most frequent finding. Bilateral synchroniom usually had a bad prognosis.

FROM THE AUTHORS' SUMMARY.

BCG DIAGNOSTIC REACTION. M. D'AVIGNON and S. NORSTEDT, Acta pædiat. **40**:70 (Jan.) 1951.

The authors have studied surveys of the literature on the subject of Koch's phenomenon, in the form described by Ustvedt as the BCG diagnostic reaction. Theoretical problems are discussed in relation to this study, and also the examination technique. The authors' material consisted of 69 children with positive reaction to tuberculin and suffering from active primary tuberculosis, thus all having a positive BCG diagnostic reaction, 104 patients with negative reaction to tuberculin and all with negative BCG diagnostic reaction, and 262 children inoculated with BCG, of whom 246 had positive reaction to tuberculin and 249 had positive BCG diagnostic reaction. Besides the theoretical interest of this reaction, attention is drawn to the possibility of utilizing it in cases in which, despite a probable tuberculous infection, the patients are insensitive to tuberculin and perhaps also, according to Ustvedt, of utilizing it for differentiation of so-called false reactions to tuberculin from specific reactions, though the authors themselves have not observed any case of this kind. The reaction might also be utilized as control of persons inoculated with BCG.

FROM THE AUTHORS' SUMMARY.

A YEAR OF TREATMENT OF TUBERCULOUS MENINGITIS. C. HOOFT and V. DENEVE, Maandschr. kindergeneesk. **19**:423 (Nov.) 1951.

One hundred forty-three children with tuberculous meningitis were treated from May 1947 to January 1951; 21 died within the first three days after admission. Of the rest 63 (50%) were surviving on July 1, 1951. In the authors' experience the intramuscular administration of paraaminosalicylic acid must be carried on without interruption for at least six months, 500 mg. daily for infants, and up to 1 gm. for older children. Streptomycin should be discontinued gradually; after six months of intensive therapy the daily dose is administered three times every second day, three times every third day, and three times every fourth day.

Special care is needed in the intrathecal administration of streptomycin: the call is for small doses (25 to 50 mg.), not too frequently; when the protein index of the cerebrospinal fluid rises, more frequent punctures are indicated, but without injection of streptomycin.

The authors' present scheme of treatment gave 72% survivals in patients over 2 years old (23 out of 32).

Unfavorable prognostic factors are low age, late diagnosis, and sensory disturbances on admission.

In a few cases other tuberculous localizations have been noted a long time after recovery from the meningitis.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

LIPOPROTEINS OF SERUM IN INFANCY AND CHILDHOOD. C. HENRY KEMPE, HENRY K. SILVER, and FRANCIS SCOTT SMYTH, J. Pediat. **40**:11 (Jan.) 1952.

Serum concentrations of lipoprotein molecules (S_f 10-20 class) are said to be associated with atherosclerosis. In this study, the values for normal male and female children were similar Values for boys were significantly lower than those previously determined for normal men. The levels for girls approximates the range for young normal women. There was no correlation between the concentrations of these lipoproteins in the sera of newborn infants and their mothers. And there was no correlation between the total serum cholesterol and the level of the S_f 10-20 class. Children can tolerate a relatively much higher intake of fat than adults without showing increases in the S_f 10-20 molecules.

MACDONALD, Pittsburgh.

LIPOPROTEINS OF SERUM IN INFANCY AND CHILDHOOD. JOHN H. CARR, C. HENRY KEMPE, and HENRY K. SILVER, J. Pediat. **40**:19 (Jan.) 1952.

Serum concentrations of lipoprotein molecules of the S_f 10-20 class in juvenile diabetics show that diabetic girls and boys have higher levels than their normal counterparts. Values for girls were higher than those for boys. However, no correlation was shown between the serum levels of these lipoproteins and (1) the duration of the diabetes, (2) the degree of control, (3) the severity of the disease, (4) serum cholesterol levels, or (5) dietary intake of fat per unit of body weight.

MACDONALD, Pittsburgh.

PLASMA THROMBOPLASTIN COMPONENT (PTC) DEFICIENCY: A NEW DISEASE RESEMBLING HEMOPHILIA. PAUL M. AGGELER, SIDNEY G. WHITE, MARY BETH GLENDENING, ERNEST W. PAGE, TILLIE B. LEAKE, and GEORGE BATES, Proc. Soc. Exper. Biol. & Med. **79**:692 (April) 1952.

A 16-year-old Caucasian boy, when an infant, had clinical and laboratory findings suggesting thrombocytopenic purpura for which a splenectomy was performed at 2 years of age. The patient has been hospitalized over 100 times because of major hemorrhagic episodes. Prolonged coagulation was markedly shortened and the hemorrhage rapidly controlled by the transfusion of whole blood, fresh or frozen plasma, or freshly lyophilized plasma; however, when the patient was given potent antihemophilic globulin coagulation time was not shortened, and this was the first suggestion that the patient did not have hemophilia. The prolonged coagulation time is accompanied by a markedly defective prothrombin utilization correctable by the addition in vivo or in vitro of small quantities of normal plasma. The patient's blood contains normal amounts of previously described coagulation factors. The coagulation effect is due to the absence from his plasma of a previously undescribed coagulation factor; this missing factor has been named plasma thromboplastin component (PTC). The substance does not accelerate a one-stage prothrombin determination. Plasma-thromboplastin deficiency resembles hemophilia clinically and in certain laboratory features but is distinguished from hemophilia in that plasma thromboplastin deficiency cannot be corrected by antihemophilic globulin, Seitz-filtered plasma, or $BaSO_4$-adsorbed plasma, (2) it can be corrected by means of normal serum or plasma and with the citrate eluate of $BaSO_4$-adsorbed plasma or serum, (3) hemophilic-deficient and plasma-thromboplastin-deficient bloods correct each other's defects.

HANSEN, Galveston, Texas.

RECURRENT NEUTROPENIA. ALAN MONCRIEFF, Arch. Dis. Childhood **26**:440 (Oct.) 1951.

A boy, aged 2 years, appeared to suffer from recurrent reductions in the polymorphonuclear white cells, associated with fever and infection. Various theories have been advanced to account for this periodic neutropenia. None of them appears to explain the phenomenon.

KELLY, Milwaukee.

PATHOGENESIS OF ESSENTIAL CHRONIC GRANULOCYTOPENIA ON BASIS OF BONE MARROW FINDINGS. C. GASSER, Helvet. paediat. acta **7**:426 (Nov.) 1952.

The author describes a new case of essential chronic (benign) granulocytopenia, discusses the bone-marrow findings and presents graphs. In the majority of cases, a shift to the left in the neutropoiesis is scarcely present. There is, however, a noticeable decrease in the segmented forms. The stab cells are not decreased and show segmental tendencies.

There is neither a disturbance in the cell multiplication by division (mitosis) nor an inhibition of their evacuation from the marrow into the blood stream. On the other hand, there is a disturbance in the maturation of the myelocytes to the segmental forms. The cause of this maturation disturbance may lie in a diencephalic disorder with a domination of the parasympathetic nervous system. The accompanying symptoms of cranial asymmetry, vegetative and allergic manifestations would agree with this hypothesis. Because of the definite peripheral lymphocytosis, the question of an abnormally strong influence of the lymphatic system also has to be considered.

Phagocytosis of the neutrophiles by the monocytes which is often found permit the hypothesis of a premature destruction of the segmental neutrophiles of possibly inferior quality immediately after their formation.

In the erythropoiesis, there is often a definite decrease in the erythroblasts. In one case acute erythroblastopenia was subsequently observed.

The platelet formation is not disturbed except in the terminal stage of one case with secondary panmyelophthisis.

FROM THE AUTHOR'S SUMMARY.

A NEW SYNDROME: LOBSTEIN'S DISEASE ASSOCIATED WITH FAMILIAL AND HEREDITARY THROMBASTHENIA OF GLANZMANN. P. P. GAUTIER and J. GUINAND-DONIOL, Schweiz. med. Wchnschr. **82**:407 (April 12) 1952.

A girl who had had melena neonatorum presented signs of osteogenesis imperfecta from the age of 6 weeks. When she was 8 months old, subcutaneous, subconjunctival, and preretinal hemorrhages occurred. There was no deafness when she was seen at the age of about 13 months. While the number of the platelets was not diminished, evidence of thrombasthenia was obtained. Blue sclerae without osseous alterations occurred on the maternal side, while formes frustes of thrombasthenia were noted on both sides.

AMBERG, Rochester, Minn.

THE LEUKOCYTIC FORMULA IN BABIES UNDER ONE YEAR OF AGE. TEODORO ZENTENO and OSCAR CORREA B., Rev. chilena pediat. **22**:135 (April) 1951.

The authors present a study concerning differential leucocyte counts in infants under 1 year of age, healthy and in good nutritional condition. The work comprises 451 cases seen in the Asylum Service of the Luis Calvo Mackenna Children's Hospital in the last six years.

During the first quarter of life the following values were found: basophiles, 0; eosinophiles, 3; myelocytes, 0; juvenile cells, 0; stab cells, 5; segmented cells, 26; lymphocytes, 60, and monocytes, 6; during the second, third, and fourth quarters, these figures, respectively were basophiles, 0, 0, 0; eosinophiles, 2, 2, 2,; myelocytes, 0, 0, 0,; juvenile cells, 0, 0, 0,; stab cells, 4, 5, 5; segmented cells, 27, 30, 30; lymphocytes, 62, 59, 58, and monocytes, 5, 4, 5. An analysis of all cases taken as a total gave the following values, with maximum and minimum levels in parentheses: basophiles, 0 (0.41-0.00); eosinophiles, 2 (7.68-0.00); myelocytes, 0 (0.69-0.00); juvenile cells, 0(1.98-0.00); stab cells, 5 (13.3-0.00); segmented cells, 28 (36.28-18.64); lymphocytes, 60 (84.46-34.90), and monocytes, 5 (12.09-0.00).

There was a striking similarity in the differential leucocyte count during the first four quarters of life. There was considerable variation in the count of stab cells, segmented cells, lymphocytes, and monocytes, findings which must be kept in mind for a correct interpretation of deviations of the number of cells from the normal.

FROM THE AUTHORS' SUMMARY.

CONTRIBUTION TO THE ETIOLOGY OF FIBROSIS OF THE MYOCARDIUM IN INFANTS. H. RUHLAND, Deutsche med. Wchnschr. **77**:332 (March 14) 1952.

An infant with atresia ani which could be relieved by surgery followed by repeated dilatations, acquired furunculosis at the age of 7 months. In the further course several skin infections occurred, the last impetiginous eczema at the age of 21 months, which cleared up. At the age of about 22 months the infant fell ill, having previously been apparently in good shape. The heart was dilated; its insufficiency improved somewhat under medication. The infant died about 4½ months later. The heart presented very advanced lesions of myocarditis interstitialis fibroplastica. It is suggested that repeated purulent skin infections may have played a decisive etiological role.

AMBERG, Rochester, Minn.

THE DIAGNOSTIC POSSIBILITIES OF THE CATHETERIZATION OF THE HEART IN CONGENITAL HEART LESIONS. A. SCHAEDE and H. LOZKES, Deutsche med. Wchnschr. **77**:454 (April 11) 1952.

The diagnostic value of the anatomical localization of the heart catheter in cases of congenital heart lesions is demonstrated on cases of open duct, isolated atrium-septal defect, faulty communication of a pulmonic vein with the right atrium, ventricular defect in tetralogy of Fallot, arteriovenous aneurysm in the right lower lobe of the lung, and a venous anomaly with aneurysmatic dilatation of the large veins entering the heart.

AMBERG, Rochester, Minn.

TREATMENT OF ANEMIA IN INFANTS AND CHILDREN WITH TRIVALENT IRON. HEINRICH WIESENER, Deutsche med. Wchnschr. **77**:623 (May 9) 1952.

Anemias of severe degrees due to iron deficiency responded well to repeated intravenous injections of trivalent iron in colloidal solution. This treatment is resorted to particularly when oral administration of bivalent iron is poorly tolerated or the resorption is deficient. Infants up to three months received 5 mg. per kilogram of body weight daily until a total of 100 mg. was reached. Older infants received 10 mg. per kilogram daily to a total of 800 mg. Young children received a total dose up to 1.5 gm. and school children up to 2 gm. Hypochromic anemias in the course of infection also responded well. In two instances, shock-like symptoms were observed.

AMBERG, Rochester, Minn.

TRAUMATIC HEART DISEASE IN A SIX-YEAR-OLD GIRL. JØRGEN VESTERDAL, Acta pædiat. **41**:185 (March) 1952.

The author reports a case of ventricular paroxysmal tachycardia combined with atrioventricular block, arising after a fist blow in the chest in a girl of 6. Sinus rhythm was obtained with quinidine. Corticotropin (ACTH) had no demonstrable effect on the scar presumably present in the right ventricle.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat, and Ear

TREATMENT OF OTITIS MEDIA CAUSED BY PSEUDOMONAS AERUGINOSA IN INFANTS WITH NEOMYCIN. A. M. LAZAR, MILTON GOLDIN, and HELEN AUERBACH, A. M. A. Arch. Otolaryng. **55**:444 (April) 1952.

Several infants with otitis media from which Pseudomonas aeruginosa bacteria were grown were treated with neomycin ear drops containing 200 units per cubic centimeter of isotonic saline solution. In addition they received 1,500 to 2,500 units of neomycin intramuscularly every three to four hours for three to four days. In all there was prompt improvement without untoward reaction.

KIMBALL, Evanston, Ill.

HEMANGIOMA OF THE LARYNX IN AN INFANT. HAROLD W. DARGEON, and JOHN F. DALY, J. Pediat. **39**:738 (Dec.) 1951.

A 3-month-old infant had progressive and eventually fatal respiratory distress after a prophylactic inoculation of diphtheria, pertussis, and tetanus vaccine. The child had a capillary hemanigoma of the larynx, the 11th such reported case in the literature, probably not a true index of the frequency of this condition.

MACDONALD, Pittsburgh.

SPECIAL TECHNIQUES IN TESTING THE HEARING OF CHILDREN. WILLIAM G. HARDY, and JOHN E. BRODLEY, J. Speech & Hearing Disorders **16**:122 (June) 1951.

Hearing tests for infants and young children must be reasonably accurate, descriptively significant, and useful. Most techniques for children do not present this kind of information except in a very limited way. Since 1947, experiments have been under way to develop "ascending" technics in audiometry together with the Fere effect and a modified form of Pavlovian conditioning. A fairly short burst of the test tone is followed in about three seconds by a mild faradic shock from the inductorium. About 8 to 12 of the combined signals are necessary to set up a conditioned-reflex arc. The shock annoys but does not hurt. Over 650 tests have been done on preschool-age children with skin-resistance responses from infants as young as 3 weeks. Retest data on some of this material shows a rather high degree of reliability, although there is a large spread in individual cases.

PALMER, Wichita, Kan.

PERCEPTIVE DEAFNESS IN CHILDHOOD. R. SCOTT-MONCRIEFF, Laryngoscope **62**:1081 (Oct.) 1952.

The incidence of severe deafness in children is roughly 1 : 300 for boys and 1 : 400 for girls. Of these twice as many have the acquired, postnatal type as the congenital type. A classification table is given for the perceptive deafnesses. Familial deafness is transmitted by the Mendelian pattern. It is a recessive characteristic and results in a developmental anomaly. Rh incompatibility may involve the cerebral cortex and cranial nerves. Maternal rubella affects the cochlear development and is the cause of 20% of infantile deafness. Poliomyelitis also behaves similarly, although the other virus diseases do not. Certain drugs may also affect the development of the cochlea. Of postnatal causes are mentioned infections (meningitis), drugs, and trauma. Diagnosis is discussed, together with methods used to recognize deafness in early childhood. Mental retardation, speech delays, and developmental word deafness are mentioned in the discussion of the differential diagnosis.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

AURICULAR SEPTAL DEFECT IN ONE OF MONOZYGOTIC TWINS. CONSTANCE C. FORSYTH and IRENE UCHIDA, Arch. Dis. Childhood **26**:587 (Dec.) 1951.

Auricular septal defect is reported in one of monozygotic twin girls, aged 6 years, her twin being clinically normal. The analysis of zygosity is based upon consideration of the fetal membranes, the blood groups and types, the digital, palmar, and plantar configurations, and other physical features. The twins came to differ in their characterization because of a variation in their experience subsequent to conception, such as differences in their circulation early in intrauterine development or some random physicochemical variation in their embryonic development.

KELLY, Milwaukee.

ACCELERATION OF DEVELOPMENT AND HYPERTROPHY OF THE TONSILS: CONTRIBUTION TO THE BIOLOGY OF THE TONSILS ACCORDING TO AGE. BERNFRIED LEIBER, Med. Klin. **47**:582 (April 25) 1952.

Like other phases of development, hypertrophy of the tonsils has accelerated within recent years. For instance, in 1925 only 0.2% of all cases of hypertrophy of the tonsils were found during the first year of life, while in 1950 the percentage was 3.6. The maximal percentage is reached at an earlier age, and the involution also occurs at an earlier age. Greater details are given in other publications.

AMBERG, Rochester, Minn.

Diseases of Lungs, Pleura and Mediastinum

ACTH IN ASPIRATION OF PEANUTS. M. K. MACGOUGAN and S. B. THORSON, Canad. M. A. J. **66**:371 (April) 1952

Because of a feeling that the extremely rapid and intense edema of the bronchial mucosa might be due to an allergy to the irritating oils in nuts, the authors used corticotropin in one

case The patient required tracheotomy because the obstruction was so severe that a bronchoscope could not be passed. After administration of corticotropin edema subsided so that the foreign body could be removed by bronchoscope.

McGUIGAN, Evanston, Ill.

Diseases of the Gastrointestinal Tract, Liver, and Peritoneum

TREATMENT OF INFANTILE DIARRHEA WITH A NEW COMBINATION OF ANTIBIOTICS. ELMER R. KADISON and MAXWELL P. BOROVSKY, J. Pediat. **38**:576 (May) 1951.

Bacitracin is active against Gram-positive cocci and bacteria, a few large viruses, and Endamoeba histolytica. Neomycin is active against a few Gram-positive but many Gram-negative bacteria, the tubercle bacillus and E. histolytica. When bacitracin and neomycin are given together a synergistic effect results. In this study, tablets containing 10,000 units of neomycin and 2,000 units of bacitracin were used. The combination was called "neobacin."

Twenty-one infants with diarrhea were given "neobacin," 1 tablet every 6 hours orally. Three of these had amebiasis and received double doses. These infants were compared with 32 controls treated with sulfadiazine, streptomycin, and penicillin. All infants received routine supportive treatment. "Neobacin" markedly depressed both Gram-positive and Gram-negative intestinal flora, the reason, perhaps, for its beneficial effect.

Infants treated with "neobacin" showed a significant reduction in duration of diarrhea as compared with the control group.

MACDONALD, Pittsburgh.

ACUTE APPENDICITIS IN CHILDREN. GEORGE B. PACKARD, and CARL H. MCLAUGHLIN, J. Pediat. **39**:708 (Dec.) 1951.

This is a report of a statistical study of 329 consecutive patients under 14 years of age. The study included a period, July, 1945, to July, 1950, when antibiotics were in general use. The operations were performed by 40 surgeons, including the resident staff. Cases were classified into three groups, simple acute appendicitis (59.2%), perforated appendicitis with local peritonitis (18.2%), and perforated appendicitis with diffuse peritonitis (4.9%). Ten and four-tenths per cent of the entire group were reported as normal appendices by the pathologist. Seven per cent of the patients were operated on during a clinically quiescent period of recurrent appendicitis.

Most of the cases (over 60%) occurred during the winter and spring. These are the seasons for respiratory infections, and this would seem to substantiate the idea that these acute infections are an etiological factor in acute appendicitis.

Twenty-five and five-tenths per cent of the entire series were children 4 years of age or under. Of the patients in this group, 60% had diffuse or local peritonitis at the time of surgery. Children over 4 years of age more frequently exhibited "typical" signs, with pain in the right lower part of the abdomen and moderate elevation of the white blood cell count. Except in the very young, this study indicates that a normal count is evidence against the existence of appendicitis.

There was only one death in the entire series.

MACDONALD, Pittsburgh.

INTESTINAL PNEUMATOSIS IN INFANTS. J. WAINWRIGHT, Arch. Dis. Childhood **26**:165 (April) 1951.

Six cases of intestinal pneumatosis in infants are reported; the lesion is not uncommon. The relationship with severe diarrhea and ulcerative enterocolitis is emphasized. The condition is thought to be produced mechanically.

KELLY, Milwaukee.

STUDIES IN COELIAC DISEASE: GLUCOSE ABSORPTION. WILFRED SHELDON and ANTOINETTE MACMAHON, Arch. Dis. Childhood **26**:450 (Oct.) 1951.

The flat blood-sugar curve after oral administration of glucose in children with celiac disease is confirmed, and evidence is produced to support the claim of previous writers that this curve tends to move toward the normal as recovery proceeds.

In normal children the blood-sugar curve shows a considerably higher rise when glucose is put into the duodenum than when it is given by mouth.

In active celiac disease, glucose put into the duodenum gives a relatively flat curve when compared with the curve in normal children. As the clinical condition improves the curve recovers toward the normal.

KELLY, Milwaukee.

PERFORATED PEPTIC ULCER IN A MONGOLOID INFANT ASSOCIATED WITH CONGENITAL DIAPHRAGMATIC HERNIA. R. SPENCER and M. MARGARET ROGERSON, Arch. Dis. Childhood **26**:569 (Dec.) 1951.

A clinical case of typical mongolism, in a child aged 4 years and 4 months, is presented. He was admitted to the hospital on account of diarrhea and vomiting. A diaphragmatic hernia was discovered. Death occurred from bronchopneumonia complicated by whooping cough. Necropsy demonstrated bronchopneumonia, diaphragmatic hernia, and perforation of a duodenal ulcer.

KELLY, Milwaukee.

THE RELATIONSHIP OF CYSTIC LESIONS OF THE ACINI OF THE PANCREAS TO AGE, CAUSE OF DEATH AND FIBROCYSTIC DISEASE IN CHILDREN. J. L. EMERY, Arch. Dis. Childhood **26**:573 (Dec.) 1951.

The pancreas was examined histologically for the presence of plugged and cystic acini in 310 necropsies at the Children's Hospital, Sheffield, England. Cysts were found in 144 (46.5%) of the cases; in small numbers in 110 (35.5%) cases, in larger numbers in 23 (7.5%) cases, and in the frank fibrocystic syndrome in 11 (3.5%). It was found that there was a marked variation of incidence with age, the incidence under 6 months being over 60% and falling to the adult level of about 20% by the age of 9 years. It was found that varying incidence with age eliminated differences in incidence apparently associated with different diseases.

After considering the experimental and other causes of cystic lesions in the acini of the pancreas, the author suggests that the high incidence of cysts in the period of most active growth may be related to the child's enhanced protein requirements at that period.

KELLY, Milwaukee.

A STUDY OF ABDOMINAL PAIN IN CHILDREN. D. J. CONWAY, Great Ormond St. J. (No. 2) 99 (Dec.) 1951.

The authors studied 243 consecutive patients who complained of abdominal pain. One of every 10 children brought to the outpatient department came with this complaint.

Attempts to clarify the etiology of abdominal pain failed. Diagnoses made in the 243 cases totaled 22 different conditions. Fourteen of the 243 patients were found to have a serious malady, i. e., pyelitis, hydronephrosis, jaundice, pleural effusion, appendicitis, brain tumor, and diabetes. It was not possible to demonstrate a different pattern of symptoms or measures which produced relief for each diagnostic group.

The author feels that present diagnostic criteria are not reliable for solving the problem of abdominal pain in 95% of the cases seen.

MCGUIGAN, Evanston, Ill.

MANAGEMENT OF ACUTE GASTRO-ENTERITIS. DAVID LAWSON, Great Ormond St. J. (No. 2) 110 (Dec.) 1951.

The author outlines in detail the routine management of gastroenteritis as practiced at the Great Ormond Street Hospital during 1948 and 1949. Close attention is paid to electrolyte and fluid balance as well as food requirements. Local infections are treated with antibacterial agents. During the neonatal period, penicillin is not used alone because of the danger of developing secondary Escherichia coli infections.

MCGUIGAN, Evanston, Ill.

INTESTINAL POLYPOSIS ASSOCIATED WITH MELANIN SPOTS OF THE ORAL MUCOSA: SYNDROME OF PUETZ. O. D. FISHER, Great Ormond St. J. (No. 2) 151 (Dec.) 1951.

A case of melanin pigmentation of the oral mucosa associated with vague abdominal pain and anemia is presented. No changes could be demonstrated in the bowel, though the author believed that the patient had the syndrome of Puetz. Five months later the patient was readmitted with intussusception. Surgery revealed four polyps in the small intestine.

McGUIGAN, Evanston, Ill.

EFFICACY OF MARCONI THERAPY IN SPASTIC STENOSIS OF THE PYLORUS IN INFANTS. G. CARDINI, Lattante **20**:603 (Oct.) 1949.

Twenty-five infants with pylorospasm and pyloric stenosis had not responded to treatment with epinephrine or with belladonna; they did show rapid and permanent relief after a course of short-wave treatments was administered.

HIGGINS, Boston.

VISUALIZING OF THE ABDOMINAL ORGANS AFTER RETROPERITONEAL INSUFFLATION AND TRANSVERSE AXIAL STRATIGRAPHY. A. SANSONE and A. DE MAESTRI, Minerva pediat. **3**:328 (June) 1951.

Interesting films by transverse axial stratigraphy following retroperitoneal insufflation are shown; the liver, spleen, and kidneys are well outlined.

HIGGINS, Boston.

VISUALIZING OF THE PANCREAS OF THE CHILD BY MEANS OF STRATIGRAPHY AND OF RETROPERITONEAL INSUFFLATION. G. SANSONE, N. MACRINI, and L. OLIVA, Minerva pediat. **3**:343 (June) 1951.

Films of four patients are shown, illustrating how a sharp, direct roentgenological visualizing of the pancreas can be obtained by stratigraphy after gastric and retroperitoneal insufflation.

HIGGINS, Boston.

STUDY OF DIGESTIVE DISTURBANCES IN INFANTS. M. GRAFFAR, Acta pædiat. belg. **4**:65, 1950.

This very exhaustive study, which occupies two entire issues of *Acta pædiatrica belgica*, describes in its first part the laboratory methods and continues with the detailed discussions of the problems of Shigella, Salmonella, Proteus, paracolon, and colon bacillus infections in infants. Each problem is illustrated by case reports and a thorough review of the literature.

Old as well as modern theories of the pathogenesis of "toxicosis" are presented in the second part of the study, and the results of examinations of the aerobic flora of the duodenum in health and disease as well as changes effected by the oral administration of streptomycin are reported.

GLASER, Jerusalem.

Nervous Diseases

ANTICONVULSANT DRUG THERAPY OF BEHAVIOR PROBLEM CHILDREN WITH ABNORMAL ELECTROENCEPHALOGRAMS. BENJAMIN PASAMANICK, A. M. A. Arch. Neurol. & Psychiat. **65**:752 (June) 1951.

The author studied 21 boys, 6 to 13 years of age, who presented behavior problems of varying types and who had abnormal electroencephalograms. Treatment with diphenylhydantoin sodium, methylphenylethylhydantoin trimethadione (mesantoin®), and phenobarbital gave uniformly disappointing results.

McGUIGAN, Evanston, Ill.

USE OF METHYLPHENYLSUCCINIMIDE IN TREATMENT OF PETIT MAL EPILEPSY. FREDERIC T. ZIMMERMAN, A. M. A. Arch. Neurol. & Psychiat. **66**:156 (Aug.) 1951.

The author reports on the use of methylphenylsuccinimide in the treatment of petit mal. Studies showed that the drug was equal to or superior to trimethadione in therapeutic effect, and far less toxic. In addition to its greater clinical effect, toxic signs were milder than with trimethadione. The drug was effective in many cases in which the other drugs had failed. No conclusions are drawn as to possible effect from prolonged use of the drug.

McGUIGAN, Evanston, Ill.

SURGICAL CARE OF THE NEUROLOGICALLY DEFECTIVE INFANT. J. MARTIN, A. M. A. Arch. Surg. **65**:150 (July) 1952.

Many physicians assume an attitude of unwarranted defeatism when dealing with a neurologically defective infant.

Martin takes issue with this undue pessimism. First, every child with a neurologic defect should be subjected to a thorough neurologic examination, using all modern technical means to determine the gross anatomic changes and disturbances of function. No matter how hopeless the situation may seem at first glance, precise diagnosis may point the way to successful surgical management. For example, an infant whose signs and symptoms suggest hopeless hydrocephalus may in reality harbor a favorable subdural hematoma, which can be cured by operation. In selected cases, internal hydrocephalus may be either arrested or improved by removal of the causative lesion or by restoration of the cerebrospinal fluid circulation. Surgical treatment of craniostenosis has given encouraging results if undertaken at an early stage. In cases of myelomeningocele operative repair is often worth while, even though there may be permanent neurologic defects. LIST, Grand Rapids, Mich. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CRANIAL CLUES TO INTRACRANIAL ABNORMALITY. WILDER PENFIELD, Am. J. Roentgenol. **67**:535 (April) 1952.

Penfield points out that it is the duty of the clinician to search for the cause of attacks in all cases of epilepsy. Each case eventually will be classified as one either of idiopathic epilepsy or of focal epilepsy. It is primarily the cases of focal epilepsy with which the paper deals. The focal seizures arise in abnormal living gray matter. They do not originate in tumors, cysts, and the like, although they may arise in the gray matter immediately adjacent to these abnormalities. The neurosurgeon who intends to treat focal epilepsy must use every available means to localize the lesion. "When he has made a reasonably accurate localization he may hope to stop the seizures completely in a little over 50 per cent of the cases and decrease the attacks in others."

Asymmetry of the cranium supplies a clue to injury to the brain which occurred during infancy and childhood, the active period of brain growth. The cranium is smaller over the damaged side, and often the paranasal sinuses and mastoid air cells become larger on the same side, as though to take up the space left by failure of growth of the damaged part of the brain.

Atrophic lesions of the brain often produce changes in the size, shape, and position of the ventricles. These changes may be demonstrated by pneumoencephalography. In some cases of damage during infancy the ventricle on the side of the lesion may become very large; in others it shows little change. Atrophic lesions acquired after brain growth is complete (i. e., in adults) regularly produce enlargement of the ventricle on the same side. The contralateral ventricle is almost always enlarged also, but to a slightly less degree.

Intracranial calcifications may be associated with focal epilepsy. Calcifications may appear in slow-growing brain tumors, tuberculomas, healed brain abscesses, and in a peculiar sort of lesion which Penfield has called "hemangioma calcificans." Occasionally actual plaques of bone may be found located in the subdural or subarachnoid spaces in cases of focal epilepsy. These are thought to be associated with previous hematomas in the same region. Trauma to the underlying area of the brain is probably caused by the same force that produced the hematoma.

Superficial cysts or tumors of the brain may make their presence known by producing thinning of the cranium which overlies them. Meningioma often causes formation of new bone in the overlying portion of the skull. When there is a deficiency in the dura, perhaps caused by

trauma or by surgery, the brain can rather quickly produce an irregular, "pebbly" erosion of the cranium overlying it. This is so even if the pia and the arachnoid lie intact between the brain and the skull. Penfield has named this defect in the skull "craniocerebral erosion." In the presence of increased intracranial pressure the erosion occurs more rapidly.

WEILAND, Grove City, Pa. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

FORAMINA PARIETALIA PERMAGNA. R. O'RAHILLY and M. J. TWOHIG, Am. J. Roentgenol. **67**:551 (April) 1952.

The parietal bone ossifies in membrane from one or more centers in the region of the future parietal eminence. The spread of ossification toward the median plane is slower in the region of the future parietal foramen. A membranous interval, called the "sagittal fontanelle," is thus left in this region. The parietal emissary vessels pass through the lateral angle of this membranous space. As ossification proceeds in this region, a parietal foramen is left as a remnant of the membranous space. Foramina parietalia permagna may be considered to arise as a delay in an otherwise normal process of ossification.

The parietal foramen is present in about 60% of persons. It is most commonly unilateral. More than 90% of human parietal foramina do not exceed 1 mm. in diameter. Large parietal foramina have been associated by various authors with cranial anomalies, such as metopism, microcephaly, synostosis of sutures, plagiocephaly, and thinness of the parietal bones.

O'Rahilly and Twohig present short reports of five cases in which large parietal foramina were found. The large foramina were an incidental postmortem finding in the first case, that of a man aged 75. The foramina in this case were bilateral, and each was approximately 1 cm. in diameter. In the other four cases the foramina were found on roentgenograms of the skull. Three of these four cases were found in one family. Reexamination of the three patients over a period of eight years showed little change in size or appearance of the large parietal foramina. The largest ones were about 3.5 cm. in diameter when measured on the roentgenograms.

WEILAND, Grove City, Pa. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EXCHANGES OF SODIUM AND POTASSIUM IN FAMILIAL PERIODIC PARALYSIS. T. S. DANOWSKI, J. R. ELKINTON, B. A. BURROWS, and A. W. WINKLER, J. Clin. Invest. **27**:65 (Jan.) 1948.

Exchanges of potassium and sodium between the extracellular and intracellular phases of body fluids were quantitated in two patients with proved familial periodic paralysis. Concentrations of Cl, Na, and K in serum and erythrocytes as well as balances of Cl, Na, K, and N were determined One patient was studied during recovery from a spontaneous attack of generalized paralysis, while the other was studied during an attack induced by KCl deprivation and administration of large doses of carbohydrate.

The data showed a sharp decline in extracellular potassium concentration. The potassium content of erythrocytes was also low. Balances of Cl, Na, K, and N in extracellular and intracellular fluid compartments were calculated. Extracellular fluid volume was determined by volume of distribution of injected mannitol, and changes in volume were computed by changes in serum-chloride concentration, body weight and urinary excretion of electrolytes. The calculations showed that during paralysis potassium shifted from the extracellular to the intracellular compartment, with resultant decline in serum-potassium concentration and diminution in K excretion. Hence, potassium balance was negative with respect to the extracellular compartment, and positive in the intracellular fluid compartment. No loss of K from the body was noted during periods of hypopotassemia. No significant changes in total body water and extracellular volume were observed.

BRODSKY, Louisville, Ky.

SHWARTZMAN PHENOMENON COMPLICATING ACUTE MENINGOCOCCEMIA WITH MENINGITIS. S. DAVID STERNBERG, BEN M. ZWEIFLER, and SEYMOUR GRUBER, J. Pediat. **38**:369 (March) 1951.

The authors describe a 7-month infant with acute meningococcemia meningitis. Generalized purpura developed, severest over the buttocks and thighs, and in these areas necrosis and sloughing eventually occurred. Treated with penicillin, sulfadiazine, aureomycin, and supportive measures, he eventually recovered. His buttocks are scarred.

MACDONALD, Pittsburgh.

TECHNIQUE OF PNEUMOENCEPHALOGRAPHY IN CHILDREN: COMPARATIVE RESULTS WITH AIR AND OXYGEN INJECTION. LOUIS CASAMAJOR, ROBERT W. LAIDLAW, and PHILIP J. KOZINN, J. Pediat. **38**:463 (April) 1951.

The authors describe a technique for pneumoencephalography in detail. They are convinced that atropine and codeine are better than morphine for preoperative medication because of the frequency of vomiting and respiratory difficulty when morphine is used. Postencephalographic courses in their patients were smoother when oxygen instead of air was injected. It should be noted that x-rays are taken immediately after injection of oxygen.

MACDONALD, Pittsburgh.

NEWER DRUGS IN THE THERAPY OF EPILEPSY. M. A. PERLSTEIN, Illinois M. J. **99**:75 (Feb.) 1951.

Phenobarbital is the drug of choice for grand mal seizures in children, and diphenylhydantoin sodium in adults, or combination of the two, according to Perlstein. Methylphenylethylhydantoin (mesantoin®) is the drug of choice when both grand mal and petit mal coexist. Bromides may be employed when none of the above are effective Trimethadione and paramethadione are the drugs of choice for petit mal. Both of these have a synergistic toxic effect with mesantoin.® Phenacemide is an all-purpose drug, being effective in psychomotor spells, where it is more efficacious than any other drug; it is also beneficial in grand mal and petit mal. Metharbital has the unique property of being more effective in organic brain disease than in the idiopathic form, and particularly in myoclonic spells.

Where single drugs are not effective, combinations may be tried, except for the previously noted contraindication to the combination of mesantoin® with trimethadione and paramethadione. The physician should be constantly aware of the toxic potentialities of the drugs he employs and alert to the occurrence of side effects. When trimethadione, paramethadione, or mesantoin® is given, periodic checks of the blood are essential. Evidence of agranulocytosis is indication for discontinuance. The control of hygienic and psychiatric factors is important as an adjunct to the drug therapy of epilepsy.

FROM THE AUTHOR'S SUMMARY.

HEREDITARY PERIODIC PARALYSIS: I. EFFECTS OF VARIOUS INDUCED CHANGES IN PHYSIOLOGICAL STATE ON PARALYTIC ATTACKS. M. R. ZIEGLER and I. MCQUARRIE, Metabolism **1**:116 (March) 1952.

Studies were performed on a 15-year-old patient suffering from hereditary periodic paralysis, with a view to determining the relationship between induced paralytic attacks and certain controllable variables. Attacks could be induced at will in the fasting state by ingestion of 150 gm. of glucose or the administration of 30 to 50 units of insulin. Characteristically the induced attacks were accompanied by a diminution in concentration of potassium and inorganic phosphorus in the serum, and symptoms could be relieved by ingestion of 5 gm. of potassium chloride. Similarly, if potassium chloride were ingested at regular intervals beginning at the time glucose or insulin was administered, attacks could be prevented completely. The ratio between amounts of ingested carbohydrate and potassium above which attacks could not be prevented appeared to be in the region of 75 to 1. Ingestion of sodium phosphate in comparable dosages and circumstances failed to prevent attacks and the accompanying hypokalemia.

Breathing mixtures of oxygen, nitrogen, and carbon dioxide, while producing slight elevations in the concentrations of glucose, potassium, and phosphorus in the serum, generally failed to relieve attacks. Inhalation of a high concentration of oxygen in one experiment, however, did coincide with marked elevation of the concentration of serum K and relief of the attack.

KAPLAN, Cincinnati.

SUBDURAL HEMATOMA IN INFANCY IN THE LIGHT OF THE LATEST THERAPY. ANNA J. SIREKOVA, Ann. pædiat. **176**:187 (March) 1951.

The problem of the subdural hematoma in infancy is briefly reviewed and the success of the surgical therapy according to Ingraham emphasized. In addition to this a case of bilateral subdural hematoma in a boy aged 4½ months is reported. The surgical treatment was carried out according to Ingraham's method. Control during the six months following the operation showed a normal mental and somatic state.

FROM THE AUTHOR'S SUMMARY.

TRYPTOPHAN TEST IN SPINAL FLUID. GERHARD STALDER, Ann. pædiat. **176**:270 (April) 1951.

Two qualitative tryptophan tests (according to Voisenet and according to Hopkins) were tried out and a quantitative method based on Eckert's reaction was evolved to estimate the tryptophan in the spinal-fluid protein.

In comparing several proteins in the highest dilutions positive reactions were obtained in thrombin and brain substance, both of human origin. In none of the cerebral fluids could measurable quantities of free tryptophan be detected. In every case of tryptophan "increase" this was due to an increase of tryptophan-containing proteins.

In 82% of all the cases of tuberculous meningitis cited (including those of the literature) there was a tryptophan-positive spinal fluid. The tryptophan test was positive in 104 of the 273 patients examined in the Basler Kinderspital; 45 of these had tuberculous meningitis, 34 showed a purulent, sanguinolent, or xanthochromatic fluid (false reaction), and 25 suffered from various other morbid states.

The tryptophan content in tuberculous meningitis varied between 0.2 and 11.7 mg. per 100 cc. of spinal fluid; the values in 100 mg. of spinal fluid protein were between 0.9 and 1.95%. In cases of meningitis of different origin the values varied between 0.2 and 2.4 mg. per 100 cc. of spinal fluid and 0.75 and 2.7% of the spinal fluid protein.

The tryptophan increase is as a rule dependent on the increase of the total proteins, but besides that a relative increase in the tryptophan content of the proteins of the spinal fluid can occur. It remains to be seen to what extent the occurrence of proteins rich in tryptophan is an indication of destructive processes in the brain.

ABILITY TO TOLERATE A SUCCINYL DERIVATIVE OF THIOSEMICARBAZONE WHEN INJECTED BY CISTERNAL PUNCTURE IN ANIMALS AND INTRATHECALLY IN HUMAN BEINGS. R. BULGARELLI, Minerva pediat. **3**:203 (April) 1951.

While thiosemicarbazone, a drug found efficacious in treating tuberculosis, is too irritating to be injected intrathecally, its succinyl derivative offered hope of its being less likely to cause an inflammatory reaction. Tests were made with animals, with normal children, and with children with tuberculous meningitis; it was found that the succinyl derivative could be injected intrathecally with safety. Its efficacy in tuberculous meningitis is not claimed from the data presented.

HIGGINS, Boston.

POSTENCEPHALITIS SYNDROME WITH LOCALIZATION IN THE CEREBELLORUBRAL SPINAL TRACT: CASE STUDY WITH OUTLINE OF TREATMENT. JOSE M. MINGO DE BENITO and MANUEL ALGORA GARCIA MORENA, Acta pediat. españ. **8**:1057 (Sept.) 1950.

This is a detailed case history of a girl of 18 months with negative family history and negative personal history until the age of 6 months. At 6 months tremors of the extremities developed, accompanied by some drowsiness.

Examination revealed mild rachitis, mild hypochromic anemia, and a lack of facial expression. Tremors were noted in repose, not only in the extremities but in muscles of the thorax and abdomen also. The extremities resisted passive motion. There was a rigidity of the spine with a slight lordosis. Pupillary reflexes were normal, as were those of deep and superficial tactile sense. Deep tendon reflexes were very exaggerated.

The ankles were so relaxed that they appeared almost flail, but the feet were held in the talipes equinovarus position.

Laboratory tests, including Wassermann test, tuberculosis tests, and urinalysis, were all negative. There was mild hypochromic anemia; the spinal fluid was under slight pressure, with some slight increase in the number of cells and albumin. Bacteriologically it was negative.

The authors discuss the anatomy and functions of the cerebellorubral spinal tract with the various anatomical divisions or nuclei and connections between these nuclei. The red nucleus especially has great importance in the production of hyperkinesia, hypotonicity, and certain metabolic disturbances.

Deiters' nucleus in this same general area regulates movements of reaction, expression, and association.

Since the child had a static tremor, hypertonicity, expressionless facial expression, retardation of walking and language, and drowsiness, the lesion was necessarily in the cerebellorubral spinal system.

The child, while not able to articulate a single word, could make some noises and could walk on tiptoes if helped by another person. The authors believe that the child had an acute infection not recognized by the mother which left this lesion in the cerebellorubral system; the post-encephalitic lesion.

Treatment with "belladenal," glutamic acid, and "pyridoxan," and hot baths improved the tremors, the mental state, and general health to some extent.

The authors give details and rationale of this treatment.

ALLEN, San Francisco.

DIAGNOSIS OF ENCEPHALOPATHOLOGY IN INFANCY. GUSTAVO L. ARIAZ ALVARINO, J. pediat. **16**:43 (April, May, June) 1950.

A review is presented of the various pathological conditions affecting the brain in infancy, with the differential diagnosis and treatment. One case is reported of what appears to be a cerebral hemorrhage at 4 months of age.

FROM THE AUTHOR'S SUMMARY.

MISLEADING RESULTS OF PNEUMOENCEPHALOGRAPHY IN AN INFANT WITH SEVERE HYPOGLYCEMIC ATTACKS. SVEN BRANDT, ERNA CHRISTENSEN and JØRGEN VESTERDAL, Acta pædiat. **41**:167 (March) 1952.

In a 5-month-old infant with a severe nonpancreatogenic hypoglycemia of unknown pathogenesis, an encephalogram through suboccipital puncture showed wide areas of air over the left hemisphere. Ventriculography performed three months later showed a moderate dilatation of the ventricular system as well as large accumulations of air over the right hemisphere. On both occasions the air was localized mostly in the subarachnoid space. Severe bilateral cortical atrophy was diagnosed from these findings. At autopsy, however, almost no atrophy was found, a result quite incompatible with the roentgenograms. This observation is in accordance with those of Zellweger and other authors. The authors conclude that subarachnoid accumulations of air, visible on the encephalogram or ventriculogram, are unreliable as a diagnostic guide in infants.

FROM THE AUTHORS' SUMMARY.

URINE RETENTION IN SPINA BIFIDA OCCULTA. H. J. BOEVE, Maandschr. v. Kindergeneesk. **20**:105 (May) 1952.

The author reports resection of the bladder neck for retention of urine in a case of spina bifida occulta.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

NEPHROTIC SYNDROME: EFFECT OF ADRENOCORTICOTROPIC HORMONE. C. M. RILEY, Pediatrics **7**:457 (April) 1951.

The effects of short-term corticotropin treatment (four to six days) in 14 patients with the nephrotic syndrome are presented. Five patients given eight courses showed complete clearing of edema in seven instances, one failing to show any response to a second course. Four patients given six courses showed significant but incomplete clearing of edema each time. Five patients showed no clinically significant response to seven courses.

The type of diuresis with regard to salt and water excretion was similar to that seen with spontaneous diuresis. In all but one instance the patients who failed to have a clinically significant response did, nevertheless, show a slight sodium diuresis after withdrawal of the drug. There were no consistent changes in the significant chemical findings in the blood, except that in most cases, regardless of clinical results, a drop in the level of total cholesterol was observed after treatment. Several patients who received sodium lactate by mouth after diuresis did not accumulate edema and had a pronounced increase in the urinary sodium. This suggests that at least temporarily their kidneys were capable of dealing with sodium in normal fashion.

The period of post-treatment studies on these patients varied from 7 to 15 months. Some of the patients have remained symptom-free; others have relapsed several times but have responded to subsequent periods of treatment; still others after early successes have failed to respond to later corticotropin administration. Only one of the group has shown clearing of the urine suggesting a permanent remission. Thus the use of this hormone at best offers only a means of controlling edema of the nephrotic syndrome. Whether its repeated use may alter the over-all prognosis can be determined only after a much longer period of observation. It should, however, prove useful in the study of the mechanism of diuresis.

FROM THE AUTHOR'S SUMMARY.

JUVENILE FAMILIAL NEPHRONOPHTHISIS. G. FANCONI, E. HANBART, A.v. ALBERTINI, E. UHLINGER, G. DOLIVO, and A. PRADER, Helvet. paediat. acta **6**:1 (Feb.) 1951

A high incidence of death from contracted kidney occurred among the young children of two families. One of these families had five children, in four of whom the condition was diagnosed with certainty, though in the fifth child the disease could only be suspected. In the second family, three of five children were affected with the disease. In all, there were eight children with this renal lesion, of whom seven were boys and one a girl.

The clinical course and history were remarkably similar in all cases. The onset is hard to determine, since the condition is very slowly progressive, the first symptoms appearing between the ages of 2 and 3 years. All the children belonging to the first family died during their sixth year.

The first symptoms consisted of polydipsia, polyuria and nycturia, the blood showing a low glucose level and persistent hyperelectrolytemia. Edema is never seen in this condition. There is no albuminuria during the early phase of the illness, and even during the late stage it never assumes any large proportions; this is in keeping with the absence of other signs of inflammatory changes.

In the history of these cases bouts of pyrexia of unknown origin are a common feature, and sometimes fits are mentioned. Very gradually signs of failure of renal glomeruli become noticeable as the residual N and inorganic p in the blood begin to rise. In the children of the second family the hyperphosphatemia produced signs of secondary hyperparathyroidism with a lowering of the serum calcium level, retardation of growth, and osteodystrophy. Decompensation in the acid-base equilibrium occurs early during the disease and is reflected in a falling alkali reserve and urinary ammonia excretion. The children succumb to silent uremia.

A high incidence of harelip and cleft palate was found to have occurred in the first family.

The histological findings were nearly identical in the cases from these two families. The primary lesion is a progressive degeneration of the renal parenchyma marked by hyaline changes in the proximal convoluted tubules and their basal membrane. The collecting tubules are usually atrophied, but sometimes they are hypertrophied instead. Hyaline degeneration of the glomeruli takes place without any evidence of inflammation, and the arterioles show no signs of sclerosis.

In one case, belonging to family Z, the anterior pituitary revealed dense eosinophilia and the parathyroid glands showed marked adenomatous hyperplasia containing some clearly differentiated cells with transparent nonstaining cytoplasm. In this case the bones showed pronounced fibroid degeneration with excessive production of osteoid tissue. The latter findings are characteristic of osteodystrophy of renal origin.

Apparently, this peculiar disease is due to early exhaustion of the renal parenchyma leading to degeneration of the nephrons. It is suggested that the disease be called either "familial juvenile nephronophthisis" or "idiopathic parenchymatous contracted kidneys."

FROM THE AUTHORS' SUMMARY.

"Benign" Pyelonephritis and Postpyelonephritic Hypertension. G. Fanconi, J. Ruegg, and E. Dieterle, Helvet. paediat. acta **6**:281 (Aug.) 1951.

The clinical picture of benign postpyelitic hypertension is shown by a case of hypertension and chronic pyelitis with symptoms of insufficiency of the distal tubule. The authors use the word "benign" because, despite continuous hypertension from the age of 11 years to the age of 30, the patient developed normally and was able to lead a normal life.

From the records of the Kinderspital Zurich the authors were able to find 10 other cases which did not all show the full syndrome. The essential symptoms are the hypertension, existing for years, and the chronic pyelonephritis. Less striking are the hyposthenuria or isosthenuria and the nocturia which can cause nocturnal enuresis and can be the first sign of the illness. Occasionally disturbances of the electrolyte pattern of the extracellular fluids occur. Pyelography often reveals a bilateral club-shaped dilatation of the calices and a shrinkage of the medullary pyramids.

The authors put forward the hypothesis that the hypertension is caused by an inflammatory irritation of the renin-producing cells of the distal tubules and not through an ischemic damage to the kidney function, after the manner of the Goldblatt experiment.

From the Authors' Summary.

Chronic Acidosis in Infants Due to Renal Tubular Deficiency: Its Association with Metastatic Calcification. James H. Hutchison and A. M. MacDonald, Acta pædiat. **40**:371 (Sept.) 1951.

In recent years a syndrome has been described in infants the outstanding features of which are hyperchloremia, metabolic acidosis and often nephrocalcinosis. The literature concerning this syndrome is reviewed. Four more infants exhibiting this syndrome have been studied. The common clinical features are anorexia, failure to thrive, dehydration, severe constipation, hypotonia, and a tendency to pass alkaline urine. In three patients, detailed biochemical studies were made. These revealed chronic acidosis, a tendency to hyperchloremia and a normal titratable acidity-ammonia ratio. During treatment with alkali, which caused marked clinical and chemical improvement, it was noted that the urine contained very large amounts of bicarbonate even in the presence of continuing acidosis. The fourth patient died. At autopsy extensive metastatic calcification was discovered affecting all the tissue elements of the lungs, the coronary vessels, and the endocardium. The kidneys showed lobulation and appeared somewhat immature, but there was no nephrocalcinosis. The glomeruli were not grossly abnormal. The outstanding feature was abnormality of the proximal convoluted tubules, many of which showed a marked thickening of the basement membrane and narrowing of the lumen, and lining cells of which were smaller and flatter than normal. This would appear to be the first case to be reported in which metastatic calcification (apart from nephrocalcinosis) has been described in the presence of tubular insufficiency without glomerular insufficiency. The cause of the acidosis and hyperchloremia is discussed. It is concluded that the basic defect is an inability of the proximal tubules to conserve bicarbonate in a normal manner.

From the Authors' Summary.

Signs of Sexual Precocity in a Male Infant Due to Estrogenic Ointment. Lennart Hesselvik, Acta pædiat. **41**:177 (March) 1952.

A boy, aged 10 months, showed progressive gynecomastia, increasing pigmentation of areolae mammae, penis, and scrotum, and growth of sexual hair. The symptoms were caused by percutaneous absorption of stilbestrol. The identical picture was demonstrated experimentally in another case. The mechanism of development of the syndrome is briefly discussed.

From the Author's Summary.

Diseases of Ductless Glands; Endocrinology

Effect of Hypophysectomy on the Biologic Decay of Thyroidal Radioiodine. Raymond V. Randall, Nona Lorenz, and A. Albert, Endocrinology **48**:339 (March) 1951.

It has long been considered that after hypophysectomy the secretion of thyroid hormone ceases or at least is greatly diminished. The evidence for this belief is inferential, consisting

chiefly of (1) the fall of plasma protein-bound iodine, the decrease in basal metabolic rate and the atrophic appearance of the thyroid after hypophysectomy in animals, and (2) the development of myxedema following pituitary failure in some patients. The biologic decay, or the rate of loss, of I^{131} from the thyroidal area of the rat is a general reflection of the endogenous secretion of thyroxine, and hence a method for measuring the effect of hypophysectomy on the rate of secretion of thyroid hormone. Results of experiments here reported indicate that the biologic decay of thyroidal I^{131} is reduced to 13 per cent of normal during the first sixteen days following hypophysectomy.

JACOBSEN, Buffalo.

INFLUENCE OF STRESS STIMULI ON LYMPHATIC TISSUE OF ADRENALECTOMIZED MICE. THOMAS F. DOUGHERTY and L. F. KUMAGAI, Endocrinology **48**:691 (June) 1951.

There is ample verification that the acute involution of lymphatic tissue associated with most stresses is a result of increased secretions of adrenocortical hormones caused by stress stimuli. However, it should be considered that stresses (defined here as stimuli which activate the mechanisms resulting in increased adrenocortical secretion) might also alter lymphatic tissue by mechanisms other than mediated by adrenocortical hormones. The occurrence of anadrenocortical responses in the complex of lymphatic tissue stress reactions can only be determined in animals deprived of their adrenal cortex, and such a study was carried out.

It was found that animals stressed 2 hours after adrenalectomy had significant lymphocytosis 2 hours later, which rose to enormous levels at 8 and 12 hours and returned to the level found in adrenalectomized nonstressed animals at 24 hours. This "lymphocytotic response" is an inverse image of the lymphopenic response of intact animals.

Lymphocytosis of stress occurred also in splenectomized adrenalectomized mice and hence was not due to evacuation of lymphocytes from the splenic reservoir. The observations show that adrenalectomy exposed heretofore unknown stress effects which are not mediated by adrenocortical hormone.

JACOBSEN, Buffalo.

STEADY STATE OF THE THYROIDAL IODINE. J. DOUGHERTY, J. GROSS, and C. P. LEBLOND, Endocrinology **48**:700 (June) 1951.

Findings of tracer work in biology are generally interpreted on the assumption that a "steady state" of the chemical processes in organs and tissues exists. An organ or tissue is said to be in a "steady state" with respect to one particular substance or metabolite when the amount of this substance or metabolite remains constant and, therefore, its rate of appearance in the organ or tissue is equal to its rate of disappearance. Such a "steady state" of the thyroidal iodine has never been demonstrated.

The series of experiments devised to study this point demonstrate that (1) the iodine content of the thyroid shows no diurnal variation, and (2) the uptake of iodine and the release of iodine containing hormone occur simultaneously, continuously, and at an approximately constant rate.

JACOBSEN, Buffalo.

PRESENCE OF FREE IODINATED COMPOUNDS IN THE THYROID AND THEIR PASSAGE INTO THE CIRCULATION. J. GROSS and C. P. LEBLOND, Endocrinology **48**:714 (June) 1951.

It is shown that thyroid extracts contain iodide, monoiodotyrosine, diiodotyrosine, thyroxine and at least two unidentified iodine-containing substances described as compounds number 1 and 3.

It is concluded that thyroglobulin, after passing from the thyroid cell into the colloid, undergoes proteolysis with the release of its iodinated components. Of these, thyroxin (and possibly the unknown compound, number 1) is excreted into the plasma.

JACOBSEN, Buffalo.

TWO CASES OF ADRENAL HYPERPLASIA WITH ADRENAL CORTICAL INSUFFICIENCY. N. E. FRANCE and CATHERINE A. NEILL, Arch. Dis. Childhood **26**:60 (Feb.) 1951.

Two female pseudohermaphrodites due to bilateral adrenal hyperplasia are reported. The first patient had severe Addisonian crises, biochemically confirmed, but the second followed a more prolonged and less severe course. The evidence that the clinical differences between the

two cases are associated with differences in the histological findings is presented. The possible significance of the recurrent cardiac irregularity in case 1 and the histological changes in the renal tubules in case 2 are discussed, and other cases of adrenocortical insufficiency due to adrenal hyperplasia found in the literature are mentioned.

KELLY, Milwaukee.

HYPOPITUITARISM IN FIRST COUSINS. DOUGLAS HUBBLE, Arch. Dis. Childhood **26**:538 (Dec.) 1951.

Criteria are suggested for the clinical diagnosis of pituitary dwarfism of which the most important are the persistence of an immature facies, the retardation of bone age by at least two years, and a height which is at least 20% below the average for coevals in the proved absence of hypothyroidism.

Two male first cousins are described, in one of whom, aged 7½ years, pituitary dwarfism was present and in the other, aged 20 years, pituitary hypogonadism with deficient urinary excretion of gonadotropins, testicular hypoplasia, eunuchoid habitus, defective secondary male sexual characters, and osteoporosis with retarded union of epiphyses could be demonstrated.

It is suggested that when other treatments have failed it is justifiable to use methyl-testosterone therapy after the age of puberty in pituitary hypogonadism and before the age of puberty in pituitary dwarfism.

KELLY, Milwaukee.

ADIPOSE GYNANDRISM AND GYNISM. S. L. SIMPSON, Proc. Roy. Soc. Med. **44**:453 (June) 1951.

The author uses the term "gynandrism" for males to indicate a mixture of female and male characteristics and the term "gynism" to indicate an accentuation of feminine characteristics. In the male, this condition is described—height above average, adiposity distributed as in Cushman's syndrome with genitals subnormal, testes late in descending, feminine type of pubic hair, feminine appearance, facies, voice, vasomotor instability, gestures, and emotions, gynecomastia, purple or red linea distensae, and cyanotic mottling of buttocks and extremities. The female has a height above average, a wide pelvis, advanced bone age and early epiphyseal union, early menstruation, and large breasts with large areolae.

This syndrome the author believes is due to a pituitary-adrenal hyperactivity which includes adrenal corticosteroids. The author has attempted by hormone assays to prove the existence of pituitary-adrenal hyperactivity. These are more tentative than the clinical facts which they attempt to explain. Further investigation along these lines is in progress. Nine photographs and two graphs are presented.

HEARD, Monterey, Calif.

LAURENCE-MOON-BIEDL SYNDROME. A. CSORBA, Confinia neurol. **10**:378, 1950.

Csorba reports cases of the complete Laurence-Moon-Biedl syndrome (retinitis pigmentosa, dystrophia adiposogenitalis, oligophrenia, and polydactyly) in three siblings. Genealogical studies suggested that the incomplete picture was present in some members of the maternal side of the family. The mother was healthy, but her sister and her grandfather had poor eyesight and oscillations of the eyes. In addition, her sister was the only plump member of a family of nine siblings and was considered the least intelligent. This kind of ancestral background has been present in other cases of the complete Laurence-Moon-Biedl syndrome.

FOLEY, Boston [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PATHOLOGIC-ANATOMIC EVALUATION OF SIXTEEN CASES OF NEUROBLASTOMA SYMPATHETICUM OF WHICH TWO WERE IN NEWBORN INFANTS. F. DIETRICH, Helvet. paediat. acta **7**:483 (Nov.) 1952.

Sixteen cases of neuroblastoma sympathicum arising from the adrenal cortex or from the sympathetic ganglion chain are described. Metastases were found chiefly in the regional lymph nodes, in the skull and skeletal system, in the lung, and in the liver. In five cases, the author observed hypertrophy of the heart, presumably due to hypertension caused by mechanical impairment of the circulation in the kidney (renal hypertension). The average age of the patients was 24.7 months, and five months was the longest interval between the appearance of the first

symptoms and death. Diagnosis was established during life in only half of the cases, four times by biopsy, three times by bone-marrow puncture, and once purely on clinical grounds. Biopsy and bone-marrow puncture are therefore of basic importance in suspected cases of neuroblastoma sympathicum.

FROM THE AUTHOR'S SUMMARY.

BODY GROWTH, BONE AND TOOTH DEVELOPMENT IN CHILDREN WITH ENDOCRINE DISEASES. A. PRADER and F. PERABO, Helvet. paediat. acta **7**:517 (Nov.) 1952.

The authors compare height age, bone age and dental age (from x-rays) in 58 children with constitutional precocious puberty, the adrenogenital syndrome, Cushing's syndrome, hypothyroidism, pituitary dwarfism, the Turner syndrome, "primordial" dwarfism, and progeria. Figure 14 summarizes the results, showing for each syndrome the mean value of height, bone, and dental age expressed in percentage of chronological age.

Bone age is influenced by endocrine disturbances to a greater extent than height age or dental age. It is most advanced in the adrenogenital syndrome and most retarded in athyroidism. In contrast to bone age and height age, dental age is relatively independent of endocrine disturbances. None of the examined syndromes showed an advanced dental age. In hypothyroidism and pituitary dwarfism dental age is retarded, but less retarded than height age and bone age.

FROM THE AUTHORS' SUMMARY.

FEMALE PSEUDOHERMAPHRODISM AND ADRENAL CORTEX. M. JACCOTTET, Schweiz. med. Wchnschr. **26**:613 (June 30) 1951.

An infant was admitted to the hospital twenty-four hours after birth. It had been registered as male. There was a structure simulating a penis and a split scrotum. The urinary outlet was at the base of the glans and no other orifice existed. A female hermaphrodism was diagnosed. From the values of potassium, sodium chloride, urea, and proteins in the serum and the morphological elements of the blood a hypofunction of the external layers of the adrenals was assumed, and a hyperactivity of the internal layer from the amounts of estrogens and 17-ketosteroids in the urine. Treatment with an adrenal cortex preparation and with sodium chloride proved of benefit. The infant died at an age of about 8 months; at autopsy a diffuse bilateral hypertrophy of the adrenal glands was found, with the glomerular zone very small. The hypertrophy, in large part, concerned the reticular zone. Normal ovaries were found with a small uterus and a vagina which became obstructed farther down.

AMBERG, Rochester, Minn.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

PURULENT ARTHRITIS (B. PYOCYANEUS). J. M. COLEMAN and F. C. LOWRY, Pediatrics **7**:347 (March) 1951.

A pyogenic arthritis, acute in character, in which Pseudomonas aeruginosa was the infecting organism, occurred in a premature white female infant confined to an incubator from birth. The infection cleared rapidly with the administration of dihydrostreptomycin intramuscularly. Its use in irrigating the joint at the time of aspiration may have aided in therapy. On the patient's discharge from the hospital, she seemed normal in every respect.

FROM THE AUTHORS' SUMMARY.

MYASTHENIA GRAVIS IN CHILDREN. W. G. WYLLIE, M. BODIAN, and N. F. ELLIOTT BURROWS, Arch. Dis. Childhood **26**:464 (Oct.) 1951.

Four cases of myasthenia gravis in childhood are described. The pathology, diagnosis, and treatment are described and discussed. Thymectomy was performed in three of the cases. The thymus as a surgical specimen is described in detail. There is an interesting discussion of the theories related to the causation of myasthenia gravis. Some form of interference with the neuromuscular transmission at the myoneural junction is the accepted cause of the muscular weakness in myasthenia gravis.

Wilson and Stoner found that the serum of a myasthenic patient not under treatment, when applied to the isolated nerve-muscle preparations of a frog, produces a block in neuromuscular transmission. The possibility, therefore, exists of a curare-like substance in the blood of the myasthenic patient which opposes neuromuscular transmission, but which can be neutralized or inhibited by the action of prostigmin. Whether the defect lies in the motor nerve end-plate itself, or in the tissue fluids surrounding it, is still undecided.

KELLY, Milwaukee.

EFFECTS OF ACTH AND CORTISONE ON STILL'S DISEASE. BERNARD SCHLESINGER, Great Ormond S. J. (No. 2) 61 (Dec.) 1951.

Review of seven cases of Still's disease indicates that results in general parallel those found in treatment of adult rheumatoid arthritis with corticotropin and cortisone. In all cases in which the treatment was given, removal of the hormone was followed by relapse. On occasions remissions were not maintained under therapy. Prolongation of therapy, in the hope that remission could be maintained until the acute process had burned itself out, led only to the conclusion that as long as replacement therapy continues the patient is not stimulated to build up his own protection. Reduction of dosage always resulted in relapse. In one case the relapse was considerably worse than the condition before treatment was begun, and this situation was not entirely improved even with resumption of the original dose.

MCGUIGAN, Evanston, Ill.

TYPUS DEGENERATIVUS AMSTELODAMENSIS (CORNELIA DE LANGE). D. P. R. KEIZER, Helvet. paediat. acta **7**:508 (Nov.) 1952.

The author describes a new typical case of the syndrome of Cornelia de Lange, typus degenerativus and Amstelodamensis (dystrophia polyepiphysaria). Its characteristics are rudimentary epiphyses, underdeveloped first metacarpal bone, and the impossibility of straightening the elbows.

FROM THE AUTHOR'S SUMMARY.

SACROCOCCIC TERATOMA, REMOVED WITH CURE. PIERRE J. ROSSELET, Schweiz. med. Wchnschr. **82**:495 (May 3) 1952.

A newborn infant presented a voluminous tumor in the sacrococcic regions which on operation was found to be composed of fibrous tissue, fatty tissue, smooth muscles, cartilage, and nervous tissue. It was removed successfully.

AMBERG, Rochester, Minn.

CORTICOTROPIN (ACTH) IN THE TREATMENT OF JUVENILE RHEUMATOID ARTHRITIS. J. VESTERDAL, O. REMVIG, and M. SPRECHLER, Acta pædiat. **41**:145 (March) 1952.

Seven patients, aged 2½ to 12 years, suffering from juvenile rheumatoid arthritis, were treated with corticotropin (ACTH), each patient receiving one to three series of injections (there was a total of 10 series). Eight of these series included remissions, but in only one case was the effect permanent (observation time was three and one-half months). This patient had very active arthritis, and he received a preliminary treatment with small doses of corticotropin; this probably caused hypertrophy of the adrenal cortex, which may account for the good response.

The administration of ascorbic acid, 5 gm. daily, and cholesterol, 1 to 1.5 gm. daily, had no demonstrable clinical effect.

Six patients had deformities. In three of these a correction of the deformities was obtained. In two of the remaining three cases, the deformities proved to be due to osseous ankylosis.

The authors are of the opinion that corticotropin is indicated in cases in which deformities are developing and also when deformities have already developed, if these have not yet been ascertained to be due to osseous ankylosis.

FROM THE AUTHORS' SUMMARY.

News and Comment

ANNOUNCEMENTS

Memorial Center for Cancer and Allied Diseases Announces Course.—The Pediatric Department of the Memorial Center for Cancer and Allied Diseases announces a comprehensive three-day course for pediatricians, general practitioners, and health officers on April 29 and 30 and May 1, 1953. Current developments and established methods in diagnosis, differential diagnosis, and management of benign and malignant tumors, Hodgkin's disease, leukemia, and reticuloendotheliosis in childhood are included. Content of the course is as follows: demonstrations; examinations of children in pediatric, surgical, chemotherapy and radiotherapy clinics; ward rounds and seminars under the direction of the staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. The fee is $35.00. Requests for further information should be addressed to Director of Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York.

Books

Dr. Howe and the Forsyth Infirmary. By Rollo Walter Brown. Price, $3.50. Pp. 182. Harvard University Press, Cambridge 38, Mass., 1952.

It would be impossible to write the life of Percy Howe and evaluate his contributions to dentistry without first becoming acquainted with the Forsyth brothers and their dental clinic for children that their philanthropy made possible.

Percy Howe would have been a success without the Forsyth brothers. At the age of 50 he was at a loss to know what to do with all the people who wished his dental service. His concern was with causes and relations and reasons. The Forsyth Infirmary made it possible to satisfy this dynamic and scientific curiosity.

It seems ironical that Scotch Forsyth brothers should leave a memorial for children to perpetuate the family name, a name that left no children. Two of the five brothers married and were childless.

During a dental appointment, lonely old James Forsyth asked Dr. Ervin A. Johnson of the Tufts Dental School, "If you had a large sum of money to leave, what would you do about it?"

Dr. Johnson knew precisely, a dental clinic for children. A board of trustees realizing they were pioneering an idea, turned to the dental world for guidance. They found little help, for they were ahead of their times. The Forsyth Infirmary building was dedicated on Nov. 24, 1914.

The infirmary served first as a service clinic, but with changing times saw the need for a research teaching program. Dr. Percy R. Howe gave up his busy practice and was made director at $50 a month.

His accomplishments in research were the result of a broad vision and a fertile scientific imagination.

This little book is a valuable adjunct to one's dental biographical library. It is well written and attractively bound. It is easy to read, for the author's style is simple and direct. The reader feels a part of the story as if he were making the rounds with Dr. Howe himself. We share the doctor's perplexities of research, we share his joys when the children crowd about him and feel the pride when the world pays homage to him.

This book should be examined by the initiate in dentistry or medicine. It will show him the value of using his time. Time is short, so very short. Percy Howe continually felt the pressure of time. When he was 80 years old and going blind he said. "Oh, if only I could have another 25 years! You see, there are a lot of things just coming through the fog, not clear as yet, for it takes time."

Perhaps the author's treatment of Dr. Howe's accomplishments are too conclusive. Dr. Howe's mind was filled with problems of dental medicine and their solutions. While so many of these problems remain unsolved, his continued research was a means rather than an end. Dental decay and pyorrhea is as much with us today, yet Percy Howe has contributed to and shaped our present-day thinking.

The author has given us an intimate picture of a very full life.

Phenol and Its Derivatives: The Relation Between Their Chemical Constitution and Their Effect on the Organism. By W. F. von Oettingen, U. S. Public Health Service. Price, $0.70. Pp. 408, with 71 tables. United States Government Printing Office, Washington, D. C., 1949.

This volume seemingly gives the complete literature on the chemistry, pharmacology, toxicology, and treatment of poisoning, stressing the therapeutic action of the many compounds derived from phenol.

As stated in the introduction, often systematic changes of the molecule have revealed certain trends with regard to physiologic or toxicologic effects. In the present work, these changes are discussed to give a better understanding of the mechanism of the action of such compounds.

There are 55 pages of references, a total of approximately 1,300. The phenolic and aldehyde acids, with the exception of salicylic acid, have such slight physiologic action that a discussion of them is therefore omitted. Salicylic acid has retained so little of the phenolic action and its literature is so extensive that it is not included in this volume. The volume is compiled by a well-known able pharmacologist and is written in a clear simple style. It should prove useful as a reference book.

The Responsiveness of Kindergarten Children to the Behavior of Their Fellows. By Esther Kite Harris. Monographs of the Society for Research in Child Development Serial No. 43, Vol. XI, No. 2. Price, $2.50. Pp. 184, with 25 graphs, 36 pictures, and 45 tables. National Research Council, 2101 Constitution Ave., N.W., Washington 25, D. C., 1948.

The responsiveness of kindergarten children to the behavior of their school companions was studied by means of a pictorial guess-who method, supplemented by individual interviews with the children, home reports, and information provided by the teachers. The pictures used each illustrate particular behavior or personality traits. The method is a modification of the thematic apperception approach suitable to kindergarten age. It reveals responsiveness to some aspects of behavior that the child could not verbalize otherwise.

The degree and quality of a child's social responsiveness is demonstrated to have little or no relationship to age within the group range, intelligence, skill in interpreting pictures, sex, or length of time he has been in the kindergarten. Only a slight relationship of social responsiveness to the child's personality make-up was indicated, the more striking observation being that aggressive, trouble-making, and nonconforming children showed little social responsiveness except to the behavior of their two or three closest friends.

This study is of value in demonstrating the practicality of a method of observing and studying the developing social reactions of small children. Since the method is simple and capable of standardization, the test can be administered by teachers and others not necessarily particularly skilled or trained in testing methods. As the author indicates, the test may be applied in study of the many factors, socioeconomic, environmental, sexual difference, that may have bearing on the development of social attitudes and responsiveness. The relationship of social responsiveness to specific personality traits of personality structure in general may also be studied.

Annual Review of Medicine. Vol. 2. Windsor C. Cutting, Editor; Henry W. Newman, Associate Editor. Price, $6. Pp. 485. Annual Reviews, Inc., Stanford, Calif., 1951.

This is the second volume of The Annual Review of Medicine in which a successful attempt is made to review for the reader in concise fashion the pertinent recent literature in 18 different fields of medicine. An idea of the variety of the material presented is revealed by such chapter headings as Infectious Diseases, Nutrition and Nutritional Disturbances, Allergy, and Radiology and Radioactivity. The comments of the authors of each section are of great value, since each

author is a recognized student of the subject he has reviewed. A valuable addition to each section is the complete bibliography which enables the reader to find quickly, if he so desires, the original article discussed in any particular section. An annotated list of reviews is presented at the end of the book in which the editor of this particular section makes his comments on each specific reference.

This volume is an excellent addition to any medical library because it allows the reader to find quickly the recent developments in a large vista of medicine with excellent editorial comment. The complete bibliography makes a more thorough study of any special subject easily accessible.

Cleft Palate and Speech. By Muriel E. Morley. Price, $3. Pp. 160, with 56 figures. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

For the speech therapist and the medical practitioner this book is a concise summary of the relation of speech treatment and its results to the palatal defect and its surgical correction.

The first three chapters present a brief review of the anatomy of the regions involved and a short review of cleft palate surgery. Chapter 4 outlines development of speech, both in normal and in cleft palate children.

The concluding sections give very detailed information on how the author valuates speech defects and what exercises and corrective measures are used to train or retrain the child to speak normally. Such lucid descriptions are refreshing to the reader accustomed to having specific therapy veiled in semisecrecy.

This book should continue to be a valuable short reference both for the speech therapist and cleft palate surgeon and a well organized source of information for the practitioner on the relation of speech and palate and lip defects.

Review of Functional Endocrinology from Birth Through Adolescence. By Nathan B. Talbot, Edna H. Sobel, Janet W. McArthur, and John D. Crawford. Price, $10. Pp. 638, with 218 illustrations. Harvard University Press, Cambridge 38, Mass., 1952.

Friends of Dr. Talbot have long known that he was writing a book on endocrinology and have waited impatiently for its publication. Its appearance this year, with his associates at the Massachusetts General Hospital, Dr. Sobel, Dr. McArthur, and Dr. Crawford as co-authors, is an event well worth the waiting. Condensed into the 638 pages of this volume is an encyclopedic amount of information concerning the role of the endocrine glands in health and disease.

The approach is refreshingly different from that of the older textbooks on this subject, most of which have followed a stereotyped pattern which carries the reader on a tour of Barnum and Bailey's freak show. In this volume, while all the gross disorders due to glandular dysfunction are adequately described, the emphasis throughout is on the functioning of endocrine-controlled systems which maintain homeostasis during the course of almost every disease the clinician is called upon to treat. The discussions of the metabolism of the electrolytes and their fluctuations under the influence of the various hormones, the methods for their study, and the interpretations of laboratory findings in exemplary cases are so concise and logical and reflect so well the reasoning of the highly-trained clinician, that students and interns will be quick to adopt this book as a metabolic "Bible" to be kept always at hand in the ward. From it they will gain a basic understanding of the endocrine glands from a physiological, functional, and dynamic point of view.

One of the most useful features of the book is the large number of case reports with discussion of the laboratory findings done in a manner which should encourage the student to form his own opinions about his clinical cases rather than look simply for textbook pictures of disease.

Where gaps in our knowledge exist the authors have attempted to fill them from their own studies, some of which have not been published elsewhere. It is quite evident throughout the book that they are speaking from their own ample experience and not merely repeating old ideas handed down from a previous generation of observers. There is noted, however, a tendency on the part of the authors to quote only from their own work. This is perhaps acceptable when the subject is not controversial, but where opinions differ it would seem desirable to mention other competent investigators who support opposed theories.

It would be surprising if a reviewer of such a monumental work could find nothing to criticize, and the following points seem to warrant mention:

1. Graphic presentations are often not used to their best advantage. Frequently charts and graphs show nothing more than has been stated in the text or simply duplicate it. For example, Section B of Figure 12 on page 76 is unnecessary. Charts on pages 56 and 57 concerning renal function are considerably more complicated than a statement of facts in the text and do not clarify the problem or aid the reader. Figure 6 on page 65 is redundant. The contents of this chart could be stated in one brief sentence. The book is full of charting of this sort.

2. In the discussion on parathyroid physiology the authors constantly refer to the average glomerular filtration rate and assume it to be 100 liters per square meter (page 54). Considerable experimental evidence would indicate that this is hardly a valid assumption, because a normal filtration rate varies widely. In this section of the book the authors quote liberally from their own work. An example of this is Figure 3, page 61, but it is impossible to tell from the chart or the text whether this represents human or animal experiments. The original reference indicates that the glomerular filtration rate was measured using endogenous creatinine excretion. Time and again it has been shown that only in entirely normal individuals is this equal to the inulin clearance and hence to the glomerular filtration rate. In the presence of hypoparathyroidism, pseudohypoparathyroidism, high and low phosphorus diets, administration of parathyroid extract, etc., there may be a marked change in the rate. It has been demonstrated, for example, that it may change as much as 50% with the administration of parathormone; hence it must be remeasured following administration of this extract. The fact that creatinine clearances are the basis for their discussion of kidney function would seem to invalidate somewhat a portion of their reasoning, such as Figure 11, page 74, and the material on pages 89 and 109.

3. A few minor statements are found which are entirely incorrect. On page 99, lines 17 to 20, features of the Fanconi syndrome are quoted from a paper the whole purpose of which was to show that the disease from which these patients were suffering was not the Fanconi syndrome. The authors obviously missed the point. A similar factual error occurs on page 82, where it is stated that calcium absorption is deficient in patients with steatorrhea because of the formation of fatty acid. Frazer, Van de Kamer, and the elder Holt have shown that this is incorrect.

These criticisms should not be allowed to weigh too heavily against the general excellence of this work. There can be no question that this is a remarkable collection of pediatric endocrine information, full of experimental observations, critical discussions, and a first-class bibliography.

Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment. By H. J. Parish, M.D., F.R.C.P.E., D.P.H. Price, $2.50. Pp. 204, with 28 illustrations, 8 photographs. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

As the subtitle indicates, this small book is not concerned about the general problem of infectious disease, but summarizes the present status of the various biological products available to the physician. The author, a research bacteriologist, has limited himself to what is essentially a source of reference regarding applied immunology. There is no attempt to discuss the broad aspects of the diseases mentioned.

This reviewer feels that the text will be of interest primarily to preclinical students and technicians. The physician has little need for a separate monograph of this type in that therapy and prophylaxis must always be considered in relation to the other aspects of disease.

Modern Dietetics. By Doris Johnson, edited by Hazel E. Munsell. Price, $4.95. Pp. 529. G. P. Putnam's Sons, 210 Madison Ave., New York, 1951.

Aided by Dr. Hazel E. Munsell, well known for her research and administrative activities in the fields of nutrition, Miss Johnson has made a comprehensive summary of material valuable to students of the art and science of dietetics. The subject matter is divided first into four major sections: Part I contains the material relating to components of diets and dietary considerations relating to age and population groups; Part II deals with the problems of diet therapy; Part III

presents principles and methods of cookery, and Part IV provides extensive tables with which to calculate food values and adequate index to the volume.

Parts I, II, and III encompass 387 pages, 41 chapters averaging less than 10 pages each. With lists of "Questions and Problems" and "References and Bibliography" after each chapter, the book is admirably adapted for use in teaching. The author has directed the book to teaching of nurses, and the first three sections are designed to meet the teaching requirements in schools of nursing, but students of home economics, dietetics, and nutrition also will find much of interest within its covers.

Every aspect of food composition, preservation, preparation, feeding, and utilization, for normal and abnormal individuals of all ages, is discussed in sufficient detail for all dietetic purposes, but attention is not diverted from the subject by extensive deviations into other fields. The text is broken frequently by headings, and the manuscript is written in a simple direct style further adding to ease in reading. A reasonable number of pertinent illustrations also are reproduced with the manuscript.

Healthy Babies: A Complete Handbook for Modern Mothers. By Josephine Hemenway Kenyon, M.D., and Ruth Kenyon Russell, M.D. Price, $3. Pp. 317. Little, Brown & Company, 34 Beacon St., Boston 6, 1951.

Kenyons' book has been a popular "baby book" since its appearance in 1934. The present fifth edition has been rewritten and revised to include sections on prenatal health of the mother and the child who is slow to develop. The text is modern in its thinking and should cause little criticism of its contents. The index is adequate and makes it easy for the mother to find any subject she wishes.

As always this book can be recommended as one of the better of the flood of "baby books."

Dentistry for Children. Edition 3. By John Charles Brauer, William W. Demeritt, L. D. Higley, Maury Massler, and Isaac Schour. Price, $10. Pp. 454, with 263 illustrations. Blakiston Company, 1012 Walnut St., Philadelphia 5, 1952.

The 3d edition of this book was published some five years after the 2d edition and some 13 years after the 1st edition. These 13 years have seen great strides made in pedodontics, to the extent that pedodontics has now become of age and stands shoulder to shoulder with the other specialties in dentistry. With these advances the author has seen fit to keep his book up-to-date so that it might be a suitable textbook for both undergraduate and graduate study.

The third edition follows rather closely the second edition in its written content and illustrations. The exceptions are (1) the chapter, "Dental Caries in the Growing Child" which has been written by Massler, and (2) a new chapter, "Removable Denture Prosthesis" by Demeritt.

In the first two chapters, practice of dentistry for children and parent and child management are well covered and should be of special interest to the young practitioner entering pedodontics.

The chapters on growth and development of the teeth and investing tissues, dental caries and infections of soft tissues, nutrition and oral disease, and the endocrine glands are extremely interesting and presented in the typical Massler-Schour manner with tables, charts, and illustrations.

The technical procedures outlined in the book are all accepted procedures and are highly practical. They are well illustrated and well explained so that their application can be made with ease and confidence.

The chapter on preventive orthodontics covers the growth of the head and face and the various changes that take place in the chewing mechanism in this period. Interesting and useful aids are given to assist nature in attaining a normal relationship of the teeth.

A feature of this edition, as well as both other editions, is the splendid bibliography found at the end of each chapter. Anyone interested in a particular phase of the subject can immediately and conveniently find where he may get further and more detailed accounts on it.

The print in the third edition is much easier to read than in the other editions, and the general composition seems improved. This book is recommended for any library where child health is concerned.

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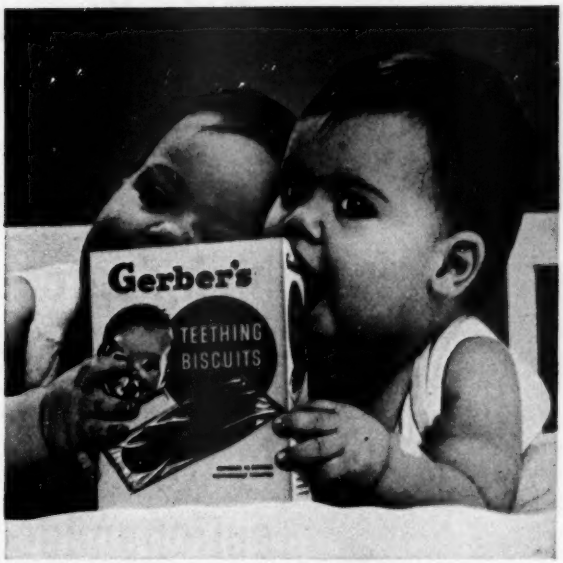

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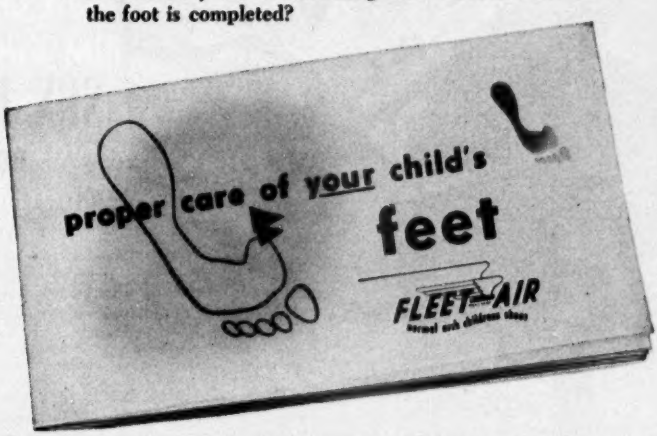

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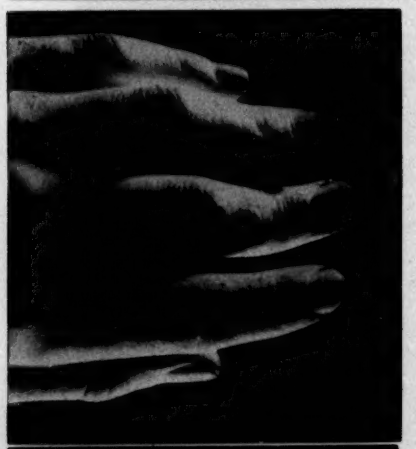

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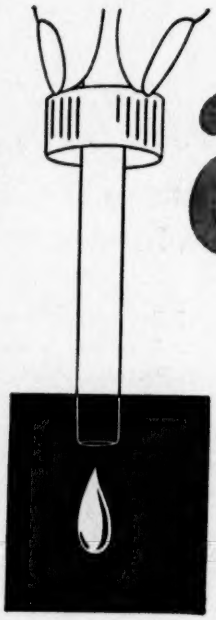
Diffusible

a+d



Drisdol with Vitamin A administered in milk becomes an integral part of the child's diet. It diffuses completely in milk, orange juice and other liquids without an oily film, does not separate, float or tend to adhere to nursing bottle or nipple. May also be given on the tongue or in solid foods.

Drisdol with Vitamin A contains per gram 50,000 units of vitamin A and 10,000 units of crystalline vitamin D_2 (calciferol). Each drop delivers 1250 vitamin A units and 250 vitamin D units.

Dosage for infants, 2 drops; for older children and adults, from 4 to 6 drops daily in milk.

Supplied in bottles of 10 cc. and 50 cc. with dropper.

Also Drisdol in Propylene Glycol (10,000 units of vitamin D_2 per gram) in bottles of 5 cc., 10 cc. and 50 cc.

To help build a sound structure and promote growth

Drisdol, trademark reg. U. S. & Canada, brand of crystalline vitamin D_2 (calciferol)

Winthrop-Stearns INC.

NEW YORK, N. Y. WINDSOR, ONT.